

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 September 2001 (07.09.2001)

PCT

(10) International Publication Number
WO 01/64639 A2

(51) International Patent Classification⁷: C07D 209/04,
401/04, A61P 29/00

(21) International Application Number: PCT/CA01/00270

(22) International Filing Date: 2 March 2001 (02.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/186,571 2 March 2000 (02.03.2000) US

(71) Applicant (for all designated States except US):
MERCK FROSST CANADA & CO. [CA/CA]: 16711
Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LABELLE, Marc
[CA/CA]; 16711 Trans-Canada Highway, Kirkland,
Québec H9H 3L1 (CA). STURINO, Claudio [CA/CA];
16711 Trans-Canada Highway, Kirkland, Québec H9H
3L1 (CA). LACHANCE, Nicolas [CA/CA]; 16711
Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA).
MACDONALD, Dwight [CA/CA]; 16711 Trans-Canada
Highway, Kirkland, Québec H9H 3L1 (CA).

(74) Agents: MURPHY, Kevin, P. et al.; Swabey Ogilvy Re-
nault, Suite 1600, 1981 McGill College Avenue, Montreal,
Québec H3A 2Y3 (CA).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

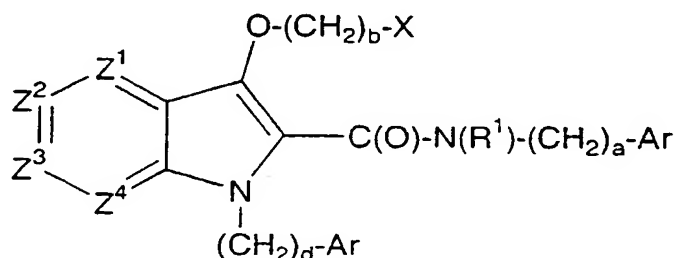
(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PDE IV INHIBITING AMIDES, COMPOSITIONS AND METHODS OF TREATMENT



(I)

(57) Abstract: Compounds represented by formula (I), as well as pharmaceutically acceptable salts and hydrates thereof are disclosed as useful for treating or preventing diseases and conditions mediated by PDE-IV. Pharmaceutical compositions and methods of treatment are also included.

WO 01/64639 A2

TITLE OF THE INVENTION
PDE IV INHIBITING AMIDES, COMPOSITIONS AND METHODS OF
TREATMENT

5 BACKGROUND OF THE INVENTION

This invention relates to compounds and pharmaceutical compositions for the treatment of diseases by raising the level of cyclic adenosine-3',5'-monophosphate (cAMP) through the inhibition of phosphodiesterase IV (PDE IV).

Many hormones and neurotransmitters modulate tissue function by elevating intracellular levels of 3', 5'-cyclic adenosine monophosphate (cAMP). The cellular levels of cAMP are regulated by mechanisms which control synthesis and breakdown. The synthesis of cAMP is controlled by adenylyl cyclase which may be directly activated by agents such as forskolin or indirectly activated by the binding of specific agonists to cell surface receptors which are coupled to adenylyl cyclase. The breakdown of cAMP is controlled by a family of phosphodiesterase (PDE) isoenzymes, which also control the breakdown of guanosine 3',5'-cyclic monophosphate (cGMP). At least seven members of the family have been described (PDE I-VII), the distribution of which varies from tissue to tissue. This suggests that specific inhibitors of PDE isoenzymes could achieve differential elevation of cAMP in different tissues [for reviews of PDE distribution, structure, function and regulation, see Beavo & Reifsnyder (1990) TIPS, 11: 150-155, Nicholson et. al. (1991) TIPS, 12: 19-27, and Torphy and Undem (1991) Thorax, 46: 512-523].

The availability of PDE isotype selective inhibitors has enabled the role of PDEs in a variety of cell types to be investigated. In particular it has been established that PDE IV controls the breakdown of cAMP in many inflammatory cells, for example, basophils (Peachell P.T. et al., (1992) J. Immunol., 148: 2503-2510) and eosinophils (Dent G. et al., (1991) Br. J. Pharmacol., 103: 1339-1346) and that inhibition of this isotype is associated with the inhibition of cell activation. Furthermore, elevation of cAMP in airway smooth muscle has a spasmolytic effect. Consequently PDE IV inhibitors are currently being developed as potential anti-inflammatory drugs particularly for the prophylaxis and treatment of asthma, by achieving both anti-inflammatory and bronchodilator effects.

The application of molecular cloning to the study of PDEs has revealed that for each isotype there may be one or more isoforms. PDE IV has been shown to exist in four isoforms (A, B, C and D) to date, each coded for by a separate gene in

both rodents (Swinnen J.V. et al., (1989) Proc. Natl. Acad. Sci. USA, 86: 5325-5329) and man (Bolger G. et al., (1993) Mol. Cell Biol., 13: 6558-6571).

The existence of multiple PDE IVs raises the prospect of obtaining inhibitors that are selective for individual isoforms, thus increasing the specificity of action of such inhibitors. This assumes that the different PDE IV isoforms are functionally distinct. Indirect evidence in support of this comes from the selective distribution of these isoforms in different tissues (Swinnen et al., 1989; Bolger et al., 1993; Obornolte R. et al., (1993) Gene, 129: 239-247, *ibid*) and the high degree of sequence conservation amongst isoforms of different species.

To date, full length cDNAs for human PDE IVA, B and D (Bolger et al., 1993 *ibid*; Obornolte et al., 1993 *ibid*; McLaughlin M. et al., (1993) J. Biol. Chem., 268: 6470-6476) and rat PDE IVA, B and D (Davis R. et al., (1989) Proc. Natl. Acad. Sci. USA, 86: 3604-3608; Swinnen J.V. et al., (1991) J. Biol. Chem., 266: 18370-18377), have been reported, enabling functional recombinant enzymes to be produced by expression of the cDNAs in an appropriate host cell. These cDNAs have been isolated by conventional hybridization methods. However using this approach, only partial cDNAs for both human and rat PDE IVC have been obtained. (Bolger et al., *ibid*. 1993 and Swinnen et al., *ibid*. 1989 and International Patent Specification No. WO 91/16457.)

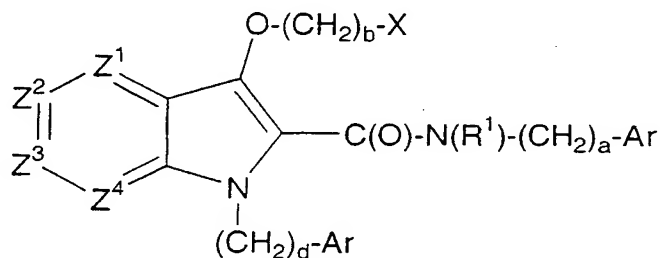
The design of PDE IV inhibitors for the treatment of inflammatory diseases such as asthma, has met with limited success to date. Many of the PDE IV inhibitors which have been synthesised have lacked potency and/or inhibit more than one type of PDE isoenzyme in a non-selective manner. PDE IV inhibitors that are relatively potent and selective for PDE IV, are reported to be emetic as well. Indeed this side effect has been so universal that experts have expressed their belief that the emesis experienced upon administration of a PDE IV inhibitor may be mechanism based.

The compounds described herein are potent inhibitors of PDE IV at concentrations that exhibit little or no inhibitory action on other PDE isoenzymes. These compounds inhibit the human recombinant PDE IV enzyme and also elevate cAMP in isolated leukocytes. Certain compounds prevent inflammation in the lungs induced by carrageenan, platelet-activating factor (PAF), interleukin-5 (IL-5) or antigen challenge. These compounds also suppress the hyperresponsiveness of airway smooth muscle seen in inflamed lungs. Advantageously, compounds according to the invention have good oral activity, and at orally effective doses exhibit little or none of

the side-effects associated with known PDE IV inhibitors, such as rolipram. The compounds of the invention are therefore of use in medicine, especially in the prophylaxis and treatment of asthma and other inflammatory conditions.

5 SUMMARY OF THE INVENTION

A compound represented by formula I:



I

or a pharmaceutically acceptable salt or hydrate thereof wherein:

- 10 one of Z¹, Z², Z³ and Z⁴ represents N or CR² and the others represent CR²;
 a represents 0 or 1;
 b represents 0, 1 or 2;
 d represents 0, 1 or 2;
 R¹ represents H, C₁₋₄alkyl or hydroxyC₁₋₄alkyl;
- 15 each R² is independently selected from the group consisting of:
 H, halo, C₁₋₈alkyl, haloC₁₋₈alkyl, hydroxyC₁₋₈alkyl, CN, Het, OR^a, OC(O)N(R^b)₂,
 NR^bC(O)R^a, C(R^a)₂CO₂R^a, C₁₋₈alkylN(R^b)₂, haloC₁₋₈alkylN(R^b)₂, CO₂R^a,
 C(O)N(R^b)₂, SO₂N(R^b)₂, S(O)_bR^d and NR^bSO₂R^d;
- 20 each R^a is independently selected from H, C₁₋₄alkyl,
 C₁₋₄alkylNHC₁₋₄alkyl, and C₁₋₄alkylN(C₁₋₄alkyl)₂, the alkyl portions of which are
 optionally substituted with 1-3 halo groups;
- 25 each R^b is selected from H and C₁₋₇ alkyl, and when two R^b's are
 present, they can be taken together and represent a fused ring system having 5-10
 members, said ring system being saturated or containing 1-4 double bonds, and
 optionally including 1-3 heteroatoms selected from O, S and NR^e;
- R^d and R^e are independently selected from Het, C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, and C₁₋₇alkyl-Het;

Het represents a 5-10 membered aromatic, partially aromatic or non-aromatic ring system containing 1-4 heteroatoms selected from O, S and N, optionally substituted on any available position with oxo, C₁₋₄ alkyl, halo, amino, hydroxyC₁₋₄ alkyl, haloC₁₋₄ alkyl and aminoC₁₋₄ alkyl;

5 X represents C₃₋₇cycloalkyl or Ar;

and each Ar is independently selected from the group consisting of: phenyl, thienyl, thiazolyl, pyridyl, oxazolyl, tetrazolyl, pyrimidinyl, pyrazinyl and pyridazinyl,

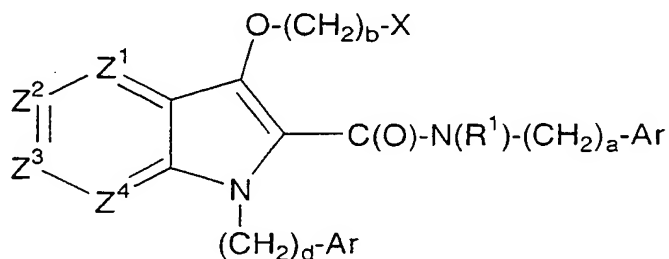
10 said Ar being optionally substituted with 1-4 members selected from: halo, hydroxy, CN, C₁₋₄alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, OC₁₋₆alkyl, OC₁₋₆haloalkyl, OC₁₋₆hydroxyalkyl, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC₁₋₆haloalkyl, C(O)NH₂, C(O)NHC₁₋₆alkyl, C(O)N(C₁₋₆alkyl)₂, C₁₋₆alkylOC₁₋₆alkylC(O)NH₂, CO₂H, CO₂C₁₋₆alkyl, NHC(O)C₁₋₆alkyl, NHC(O)OC₁₋₆alkyl, and SO₂C₁₋₆alkyl.

15 Pharmaceutical compositions and methods of treatment are also included.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses compounds represented by formula I:

20



as well as pharmaceutically acceptable salts and hydrates thereof wherein:
one of Z¹, Z², Z³ and Z⁴ represents N or CR² and the others represent CR²;

25 a represents 0 or 1;

b represents 0, 1 or 2;

d represents 0, 1 or 2;

R¹ represents H, C₁₋₄alkyl or hydroxyC₁₋₄alkyl;

each R² is independently selected from the group consisting of:

H, halo, C₁₋₈alkyl, haloC₁₋₈alkyl, hydroxyC₁₋₈alkyl, CN, Het, OR^a, OC(O)N(R^b)₂, NR^bC(O)R^a, C(R^a)₂CO₂R^a, C₁₋₈alkylN(R^b)₂, haloC₁₋₈alkylN(R^b)₂, CO₂R^a, C(O)N(R^b)₂, SO₂N(R^b)₂, S(O)_bR^d and NR^bSO₂R^d;

- each R^a is independently selected from H, C₁₋₄alkyl,
5 C₁₋₄alkylNHC₁₋₄alkyl, and C₁₋₄alkylN(C₁₋₄alkyl)₂, the alkyl portions of which are optionally substituted with 1-3 halo groups;

- each R^b is selected from H and C₁₋₇ alkyl, and when two R^b's are present, they can be taken together and represent a fused ring system having 5-10 members, said ring system being saturated or containing 1-4 double bonds, and
10 optionally including 1-3 heteroatoms selected from O, S and NR^e;

R^d and R^e are independently selected from Het, C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, and C₁₋₇alkyl-Het;

- Het represents a 5-10 membered aromatic, partially aromatic or non-aromatic ring system containing 1-4 heteroatoms selected from O, S and N, optionally
15 substituted on any available position with oxo, C₁₋₄ alkyl, halo, amino, hydroxyC₁₋₄ alkyl, haloC₁₋₄ alkyl and aminoC₁₋₄ alkyl;

X represents C₃₋₇cycloalkyl or Ar;

- and each Ar is independently selected from the group consisting of:
phenyl, thienyl, thiazolyl, pyridyl, oxazolyl, tetrazolyl, pyrimidinyl, pyrazinyl and
20 pyridazinyl,

- said Ar being optionally substituted with 1-4 members selected from:
halo, hydroxy, CN, C₁₋₄alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, OC₁₋₆alkyl,
OC₁₋₆haloalkyl, OC₁₋₆hydroxyalkyl, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC₁₋₆haloalkyl, C(O)NH₂, C(O)NHC₁₋₆alkyl, C(O)N(C₁₋₆alkyl)₂, C₁₋₆alkylOC₁₋₆alkylC(O)NH₂, CO₂H, CO₂C₁₋₆alkyl, NHC(O)C₁₋₆alkyl, NHC(O)OC₁₋₆alkyl, and
25 SO₂C₁₋₆alkyl.

As used herein, the following terms and definitions apply.

- Alkyl includes straight, branched and cyclic groups containing the indicated number of carbon atoms. If no number is specified, C₁₋₆alkyl is
30 appropriate.

Alkenyl refers to a carbon containing group having from 2-7 carbon atoms unless otherwise indicated, and 1-3 carbon-carbon double bonds. It can be straight, branched or cyclic as appropriate.

Alkynyl refers to a carbon containing group having from 2-7 carbon atoms, and 1-3 carbon-carbon triple bonds. It can be straight, branched or cyclic.

Halo includes F, I, Br and Cl. When haloalkyl is indicated, this includes monohalogenated alkyl groups containing the indicated number of carbon atoms, dihalo, trihalo, etc. up to perhaloalkyl groups.

Het represents a 5-10 membered aromatic, partially aromatic or non-aromatic ring system containing 1-4 heteroatoms selected from O, S and N, optionally substituted on any available position with oxo, C₁₋₄ alkyl, halo, amino, hydroxyC₁₋₄ alkyl, haloC₁₋₄ alkyl and aminoC₁₋₄ alkyl. Thus, examples of Het include well known heteroaryl rings, such as pyridine, pyrrole, pyrimidine, imidazole, triazole, tetrazole, and the like, as well as non-aromatic rings, such as piperidine, pyrrolidine and the like.

Ar is an aromatic ring and is selected from the group consisting of: phenyl, thienyl, thiazolyl, pyridyl, oxazolyl, tetrazolyl, pyrimidinyl, pyrazinyl and pyridazinyl. The Ar moiety is optionally substituted with 1-4 members selected from: halo, hydroxy, CN, C₁₋₄alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, OC₁₋₆alkyl, OC₁₋₆haloalkyl, OC₁₋₆hydroxyalkyl, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC₁₋₆haloalkyl, CN, C(O)NH₂, C(O)NHC₁₋₆alkyl, C(O)N(C₁₋₆alkyl)₂, C₁₋₆alkylOC₁₋₆alkylC(O)NH₂, CO₂H, CO₂C₁₋₆alkyl, NHC(O)C₁₋₆alkyl, C₁₋₆alkylOC(O)NH and SO₂C₁₋₆alkyl.

The following abbreviations have the indicated meanings:

Ac	=	acetyl
Bn	=	benzyl
cAMP	=	cyclic adenosine-3',5'-monophosphate
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	=	diisobutylaluminum hydride
DMAP	=	4-(dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
Et ₃ N	=	triethylamine
GST	=	glutathione transferase
LDA	=	lithium diisopropylamide
m-CPBA	=	metachloroperbenzoic acid
MMPP	=	monoperoxyphthalic acid
MPPM	=	monoperoxyphthalic acid, magnesium salt 6H ₂ O

Ms	=	methanesulfonyl = mesyl = SO ₂ Me
MsO	=	methanesulfonate = mesylate
NSAID	=	non-steroidal anti-inflammatory drug
o-Tol	=	ortho-tolyl
OXONE®	=	2KHSO ₅ •KHSO ₄ •K ₂ SO ₄
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
PDE		phosphodiesterase
Ph	=	phenyl
Phe	=	benzenediyl
PMB	=	para-methoxybenzyl
Pye	=	pyridinediyl
r.t.	=	room temperature
rac.	=	racemic
SAM	=	aminosulfonyl or sulfonamide or SO ₂ NH ₂
SEM	=	2-(trimethylsilyl)ethoxymethoxy
SPA	=	scintillation proximity assay
TBAF	=	tetra-n-butylammonium fluoride
Th	=	2- or 3-thienyl
TFA	=	trifluoroacetic acid
TFAA	=	trifluoroacetic acid anhydride
THF	=	tetrahydrofuran
Thi	=	thiophenediyl
TLC	=	thin layer chromatography
TMS-CF ₃	=	trimethyl(trifluoromethyl)silane
TMS-CN	=	trimethylsilyl cyanide
Tz	=	1H (or 2H)-tetrazol-5-yl
C ₃ H ₅	=	allyl

Alkyl Group Abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl

n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

In one aspect of the invention that is of interest, all four of Z¹, Z², Z³ and Z⁴ represent CR². Within this aspect of the invention, all other variables are as originally defined.

5 In another aspect of the invention that is of interest, b represents 0 or 1. Within this aspect of the invention, all other variables are as originally defined.

In another aspect of the invention, d represents 1. Within this aspect of the invention, all other variables are as originally defined.

10 In another aspect of the invention, R¹ represents H or CH₃. Within this aspect of the invention, all other variables are as originally defined.

In another aspect of the invention, each R² is independently selected from the group consisting of H, C₁-galkyl, hydroxyC₁-galkyl, CO₂R^a, C₁-galkylN(R^b)₂ and C(O)N(R^b)₂. R^b is selected from H and C₁₋₃ alkyl. Within this aspect of the invention, all other variables are as originally defined.

15 In another aspect of the invention, X represents Ar and Ar is independently selected from the group consisting of: phenyl, pyridyl and tetrazolyl, said Ar being optionally substituted with 1-4 members selected from: halo, CN, C₁₋₄alkyl, C₁₋₆haloalkyl, OC₁₋₆alkyl, OC₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, C(O)NH₂, C(O)NHC₁₋₆alkyl, C(O)N(C₁₋₆alkyl)₂, CO₂H, CO₂C₁₋₆alkyl, 20 NHC(O)C₁₋₆alkyl, NHC(O)OC₁₋₆alkyl and SO₂C₁₋₆alkyl. Within this aspect of the invention, all other variables are as originally defined.

A subset of compounds that is of particular interest relates to compounds of formula I wherein:

Z¹, Z², Z³ and Z⁴ represent CR²;

each R^2 is independently selected from the group consisting of H, C_1 -galkyl, hydroxy C_1 -galkyl, CO_2R^a , C_1 -galkyl $N(R^b)_2$ and $C(O)N(R^b)_2$ wherein R^b is selected from H and C_1 -3 alkyl;

b represents 0 or 1;

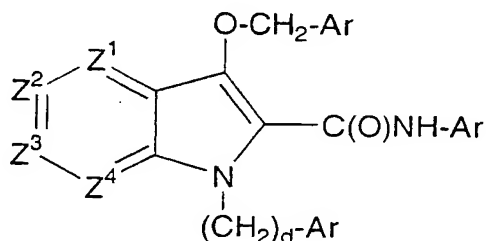
5 d represents 1;

R^1 represents H or CH_3 ;

X represents Ar and

Ar is independently selected from the group consisting of: phenyl, pyridyl and tetrazolyl, said Ar being optionally substituted with 1-4 members selected from: halo, CN, C_1 -4alkyl, C_1 -6haloalkyl, OC_1 -6alkyl, OC_1 -6haloalkyl, C_1 -6hydroxyalkyl, $C(O)NH_2$, $C(O)NHC_1$ -6alkyl, $C(O)N(C_1$ -6alkyl) $_2$, CO_2H , CO_2C_1 -6alkyl, $NHC(O)C_1$ -6alkyl, $NHC(O)OC_1$ -6alkyl and SO_2C_1 -6alkyl. Within this aspect of the invention, all other variables are as originally defined.

15 A further subset of compounds of the invention that is of interest is represented by Formula Ia:



Ia

Within this subset, all variables are as originally defined.

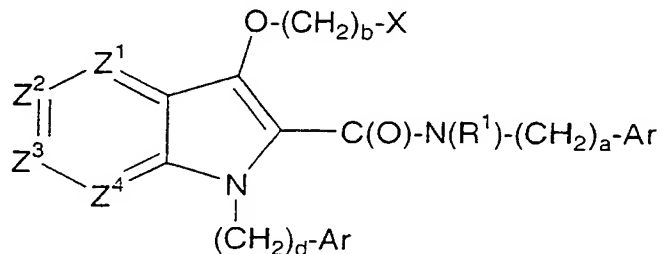
20 More particularly, a subset of compounds that is of interest relates to compounds of formula Ia wherein Z^1 , Z^2 , Z^3 and Z^4 represent CR^2 . Within this subset, all variables are as originally defined.

More particularly, a subset of compounds that is of interest relates to compounds of formula Ia wherein each R^2 is independently selected from the group consisting of H, C_1 -galkyl, hydroxy C_1 -galkyl, CO_2R^a , C_1 -galkyl $N(R^b)_2$ and $C(O)N(R^b)_2$ wherein R^a is independently selected from H and C_1 -4alkyl, and R^b is selected from H and C_1 -3 alkyl.

25 More particularly, a subset of compounds that is of interest relates to compounds of formula Ia wherein each Ar is selected from phenyl, pyridyl and

- tetrazolyl, optionally substituted with 1-4 members selected from: halo, CN, C₁-4alkyl, C₁-6haloalkyl, OC₁-6alkyl, OC₁-6haloalkyl, C₁-6hydroxyalkyl, C(O)NH₂, C(O)NHC₁-6alkyl, C(O)N(C₁-6alkyl)₂, CO₂H, CO₂C₁-6alkyl, NHC(O)C₁-6alkyl, NHC(O)OC₁-6alkyl and SO₂C₁-6alkyl. Within this aspect of the invention, all other
- 5 variables are as originally defined.

Examples of compounds falling within the present invention include the following:



Cpd	Z's	(CH ₂) _b -(O) _a -(CH ₂) _b -X	N(R ¹)(CH ₂) _a -Ar	(CH ₂) _d -Ar
1	CH	OCH ₂ -Phe-4-F	N(Me)-3-Pyr	Bnzl
2	CH	OCH ₂ -Phe-4-F	N(Me)-4-Pyr	Bnzl
3	CH	OCH ₂ -Phe-4-F	N(Me)-Phe-3,4-di- OMe	Bnzl
4	CH	OCH ₂ -Phe-4-F	N(Me)-Phe-3,4-di- F	Bnzl
5	CH	OCH ₂ -Phe-4-F	N(Me)-5-Pyr-2- OMe	Bnzl
6	CH	OCH ₂ -Phe-4-F	N(Me)-5-tetrazolyl	Bnzl
7	CH	OCH ₂ -Phe-4-F	N(Me)-4-Pyr-2- OMe	Bnzl
8	CH	OCH ₂ -Phe-4-F	N(Me)-5-Pyr-2-CN	Bnzl
9	CH	OCH ₂ -Phe-4-F	N(Me)-4-Pyr-2- OMe	Bnzl
10	CH	O-Bnzl	NH-Phe-3,4-di- OMe	Bnzl-4-F
11	CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
12	CH	OCH ₂ -Phe-3-OCF ₂ H	NH-3-Pyr	Bnzl-3- OCF ₂ H

13	CH	OCH ₂ -Phe-3-OCF ₂ H	NH-4-Pyr	Bnzl-3-OCF ₂ H
14	CH	OCH ₂ -Phe-3-OCF ₂ H	NH-Phe-3,4-di-OMe	Bnzl-3-OCF ₂ H
15	CH	OCH ₂ -Phe-3-OCF ₂ H	NH-Phe-3,4-di-F	Bnzl-3-OCF ₂ H
16	CH	O-Bnzl	NH-3-Pyr	Bnzl-4-OCF ₂ H
17	CH	OCH ₂ -Phe-3-OMe	NH-3-Pyr	Bnzl-4-OCF ₂ H
18	CH	OCH ₂ -Phe-3-OMe	NH-5-tetrazolyl	Bnzl-4-OCF ₂ H
19	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr-2-OMe	Bnzl-4-OCF ₂ H
20	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr	Bnzl-4-OCF ₂ H
21	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr-2-NHC(O)Me	Bnzl-4-OCF ₂ H
22	CH	OCH ₂ -Phe-3-OMe	NH-3-Pyr	Bnzl-4-F
23	CH	OCH ₂ -Phe-3-OMe	NH-5-tetrazolyl	Bnzl-4-F
24	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr-2-OMe	Bnzl-4-F
25	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr	Bnzl-4-F
26	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr-2-NHC(O)Me	Bnzl-4-F
27	CH	OCH ₂ -Phe-3-OMe	NH-5-pyrimidinyl	Bnzl-4-F
28	CH	O-Bnzl	NH-3-Pyr	Bnzl-3,4-di-F
29	CH	O-Bnzl	NH-4-Pyr	Bnzl-3,4-di-F
30	CH	O-Bnzl	NH-Phe-3,4-di-OMe	Bnzl-3,4-di-F
31	CH	O-Bnzl	NH-Phe-3,4-di-F	Bnzl-3,4-di-F

32	CH	O-Bnzl	NH-5-Pyr-2-OMe	Bnzl-3,4-di-F
33	CH	O-Bnzl	NH-5-tetrazolyl	Bnzl-3,4-di-F
34	CH	O-Bnzl	NH-4-Pyr-2-OMe	Bnzl-3,4-di-F
35	CH	O-Bnzl	NH-5-Pyr-2-CN	Bnzl-3,4-di-F
36	CH	O-Bnzl	NH-5-Pyr-2-NHC(O)Me	Bnzl-3,4-di-F
37	CH	OCH ₂ -4-Pyr	NH-3-Pyr	Bnzl-4-CF ₃
38	CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
39	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-OMe	Bnzl-4-CF ₃
40	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-F	Bnzl-4-CF ₃
41	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-OMe	Bnzl-4-CF ₃
42	CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
43	CH	OCH ₂ -4-Pyr	NH-4-Pyr-2-OMe	Bnzl-4-CF ₃
44	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-CN	Bnzl-4-CF ₃
45	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-NHC(O)Me	Bnzl-4-CF ₃
46	CH	OCH ₂ -4-Pyr	NH-3-Pyr	Bnzl
47	CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl
48	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-OMe	Bnzl
49	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-F	Bnzl
50	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-OMe	Bnzl
51	CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl
52	CH	OCH ₂ -4-Pyr	NH-4-Pyr-2-OMe	Bnzl
53	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-CN	Bnzl
54	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-NHC(O)Me	Bnzl
55	CH	OCH ₂ -4-Pyr	NH-4-Pyr-2-NHC(O)OEt	Bnzl

56	CH	O-Bnzl	NH-3-Pyr	Bnzl
57	CH	O-Bnzl	NH-4-Pyr	Bnzl
58	CH	O-Bnzl	NH-Phe-3,4-di- OMe	Bnzl
59	Z ¹ =N, all others =CH	O-Bnzl	NH-Phe-3,4-di-F	Bnzl
60	Z ¹ =N, all others =CH	O-Bnzl	NH-5-Pyr-2-OMe	Bnzl
61	CH	O-Bnzl	NH-5-tetrazolyl	Bnzl
62	CH	O-Bnzl	NH-4-Pyr-2-OMe	Bnzl
63	CH	O-Bnzl	NH-5-Pyr-2-CN	Bnzl
64	CH	O-Bnzl	NH-5-Pyr-2- NHC(O)Me	Bnzl
65	CH	O-Bnzl	NH-4-Pyr-2- NHC(O)OEt	Bnzl
66	CH	OCH ₂ -4-Pyr	NH-3-Pyr	Bnzl-4- OCF ₂ H
67	CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4- OCF ₂ H
68	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di- OMe	Bnzl-4- OCF ₂ H
69	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-F	Bnzl-4- OCF ₂ H
70	Z ¹ =N, all others =CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-OMe	Bnzl-4- OCF ₂ H
71	Z ¹ =N, all others =CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4- OCF ₂ H
72	Z ¹ =N, all others =CH	OCH ₂ -4-Pyr	NH-4-Pyr-2-OMe	Bnzl-4- OCF ₂ H
73	CH	O-Bnzl	NH-3-Pyr	Bnzl-4-Me
74	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-CN	Bnzl-4- OCF ₂ H
75	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2- NHC(O)Me	Bnzl-4- OCF ₂ H

76	$Z^4 =$ CC(Me) ₂ OH all others=CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
77	$Z^4 =$ CCO ₂ H all others=CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
78	$Z^4 =$ CCH ₂ NMe ₂ all others=CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
79	$Z^4 =$ CC(O)NMe ₂ all others=CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
80	$Z^4 =$ CBr all others=CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
81	$Z^4 =$ CSO ₂ NH ₂ all others=CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
82	$Z^1 =$ CC(Me) ₂ OH all others=CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
83	$Z^1 =$ CCO ₂ H all others=CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
84	$Z^1 =$ CCH ₂ NMe ₂ all others=CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
85	$Z^1 =$ CC(O)NMe ₂ all others=CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
86	$Z^1 =$ CBr all others=CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃

87	$Z^1 =$ CSO_2NH_2 all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-5-tetrazolyl	Bnzl-4- CF_3
88	$Z^1 =$ $\text{CC}(\text{Me})_2\text{OH}$ all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
89	$Z^1 =$ CCO_2H all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
90	$Z^1 =$ CCH_2NMe_2 all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
91	$Z^1 =$ $\text{CC}(\text{O})\text{NMe}_2$ all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
92	$Z^1 = \text{CBr}$ all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
93	$Z^1 =$ CSO_2NH_2 all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
94	$Z^1 =$ $\text{CC}(\text{Me})_2\text{OH}$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
95	$Z^1 =$ CCO_2H all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
96	$Z^1 =$ CCH_2NMe_2 all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
97	$Z^1 =$ $\text{CC}(\text{O})\text{NMe}_2$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F

98	$Z^1 = \text{CBr}$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
99	$Z^1 =$ CSO_2NH_2 all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
100	$Z^4 =$ $\text{CC}(\text{Me})_2\text{OH}$ all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
101	$Z^4 =$ CCO_2H all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
102	$Z^4 =$ CCH_2NMe_2 all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
103	$Z^4 =$ $\text{CC}(\text{O})\text{NMe}_2$ all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
104	$Z^4 = \text{CBr}$ all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
105	$Z^4 =$ CSO_2NH_2 all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
106	$Z^4 =$ $\text{CC}(\text{Me})_2\text{OH}$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
107	$Z^4 =$ CCO_2H all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
108	$Z^4 =$ CCH_2NMe_2 all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F

109	$Z^4=$ CC(O)NMe ₂ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
110	$Z^4=$ CBr all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
111	$Z^4=$ CSO ₂ NH ₂ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
112	$Z^3=$ CC(Me) ₂ OH all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
113	$Z^3=$ CCO ₂ H all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
114	$Z^3=$ CCH ₂ NMe ₂ all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
115	$Z^3=$ CC(O)NMe ₂ all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
116	$Z^3=$ CBr all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
117	$Z^3=$ CSO ₂ NH ₂ all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
118	$Z^3=$ CC(Me) ₂ OH all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
119	$Z^3=$ CCO ₂ H all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
120	$Z^3=$ CCH ₂ NMe ₂ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F

121	$Z^3=$ CC(O)NMe ₂ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
122	$Z^3=$ CBr all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
123	$Z^3=$ CSO ₂ NH ₂ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
124	$Z^2=$ CC(Me) ₂ OH all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
125	$Z^2=$ CCO ₂ H all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
126	$Z^2=$ CCH ₂ NMe ₂ all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
127	$Z^2=$ CC(O)NMe ₂ all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
128	$Z^2=$ CBr all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
129	$Z^2=$ CSO ₂ NH ₂ all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
130	$Z^2=$ CC(Me) ₂ OH all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
131	$Z^2=$ CCO ₂ H all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F

132	$Z^2 =$ CCH_2NMe_2 2 all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
133	$Z^2 =$ $CC(O)NMe_2$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
134	$Z^2 = CBr$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
135	$Z^2 =$ CSO_2NH_2 all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
136	CH	O-Bnzl	NH-3-Pyr	Bnzl-4- $C(Me)_2-OH$
137	CH	$OCH_2-3-Pyr$	NH-3-Pyr	Bnzl-4-F
138	CH	$OCH_2-3-Pyr$	NH-4-Pyr	Bnzl-4-F
139	CH	$OCH_2-3-Pyr$	NH-Phe-3,4-di- OMe	Bnzl-4-F
140	CH	$OCH_2-3-Pyr$	NH-Phe-3,4-di-F	Bnzl-4-F
141	CH	$OCH_2-3-Pyr$	NH-5-Pyr-2-OMe	Bnzl-4-F
142	CH	O-Bnzl	NH-3-Pyr	Bnzl-4- CO_2Me
143	CH	$OCH_2-3-Pyr$	NH-5-tetrazolyl	Bnzl-4-F
144	CH	$OCH_2-3-Pyr$	NH-4-Pyr-2-OMe	Bnzl-4-F
145	CH	$OCH_2-3-Pyr$	NH-5-Pyr-2-CN	Bnzl-4-F
146	CH	$OCH_2-3-Pyr$	NH-5-Pyr-2- $NHC(O)Me$	Bnzl-4-F
147	CH	O-Bnzl	NH-Phe-3- SO_2Me	Bnzl-4-F
148	CH	O-Bnzl	NH-3-Pyr	Bnzl-4- CF_3
149	CH	O- CH_2-cPr	NH-Phe-3,4-di- OMe	Bnzl-4-t-Bu
150	CH	O- CH_2-cPr	NH-5-tetrazolyl	Bnzl-4-t-Bu
151	CH	O- CH_2-cPr	NH-4-Pyr-2-OMe	Bnzl-4-t-Bu
152	CH	O- CH_2-cPr	NH-5-Pyr-2-OMe	Bnzl-4-t-Bu

153	CH	O-CH ₂ -cPr	NH-4-Pyr-2-NHC(O)OEt	Bnzl-4-t-Bu
154	CH	O-CH ₂ -cPr	NH-3-Pyr	Bnzl-4-F
155	CH	O-CH ₂ -cPr	NH-4-Pyr	Bnzl-4-F
156	CH	O-CH ₂ -cPr	NH-Phe-3,4-di-OMe	Bnzl-4-F
157	CH	O-CH ₂ -cPr	NH-Phe-3,4-di-F	Bnzl-4-F
158	CH	O-CH ₂ -cPr	NH-5-Pyr-2-OMe	Bnzl-4-F
159	CH	O-CH ₂ -cPr	NH-5-tetrazolyl	Bnzl-4-F
160	CH	O-CH ₂ -cPr	NH-4-Pyr-2-OMe	Bnzl-4-F
161	CH	O-CH ₂ -cPr	NH-5-Pyr-2-NHC(O)Me	Bnzl-4-F
162	CH	OCH ₂ -4-Pyr	NH-3-Pyr	Bnzl-4-F
163	CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-F
164	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-OMe	Bnzl-4-F
165	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-F	Bnzl-4-F
166	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-OMe	Bnzl-4-F
167	CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-F
168	CH	OCH ₂ -4-Pyr	NH-4-Pyr-2-OMe	Bnzl-4-F
169	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-CN	Bnzl-4-F
170	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-NHC(O)Me	Bnzl-4-F
171	CH	OCH ₂ -4-Pyr	NH-4-Pyr-2-NHC(O)OEt	Bnzl-4-F
172	CH	O-Bnzl	NH-3-Pyr	Bnzl-4-t-Bu
173	CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
174	CH	O-Bnzl	NH-4-Pyr	Bnzl-4-F
175	CH	O-Bnzl	NH-Phe-3,4-di-OMe	Bnzl-4-F
176	CH	O-Bnzl	NH-Phe-3,4-di-F	Bnzl-4-F
177	CH	O-Bnzl	NH-5-Pyr-2-OMe	Bnzl-4-F
178	CH	O-Bnzl	NH-5-tetrazolyl	Bnzl-4-F
179	CH	O-Bnzl	NH-4-Pyr-2-OMe	Bnzl-4-F

180	CH	O-Bnzl	NH-5-Pyr-2-CN	Bnzl-4-F
181	CH	O-Bnzl	NH-5-Pyr-2-NHC(O)Me	Bnzl-4-F
182	CH	O-Bnzl	NH-4-Pyr-2-NHC(O)OEt	Bnzl-4-F
183	CH	O-Bnzl	N(Me)-3-Pyr	Bnzl-4-F
184	CH	O-Bnzl	N(Me)-3-Pyr	Bnzl-4-CF ₃
185	CH	O-Bnzl	3-pyridylmethyl	Bnzl-4-F
186	CH	O-Bnzl	4-pyridylmethyl	Bnzl-4-F
Phe=phenyl, Bzyl=benzyl, Pyr=pyridyl				

In another embodiment, the invention encompasses a pharmaceutical composition comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

5 Within this embodiment, the invention encompasses pharmaceutical compositions for the treatment or prevention of diseases or conditions benefited by the inhibition of PDE IV, resulting in an elevation of cAMP, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described above.

10 The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

15 The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from
20 pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-

ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

5 The compounds described herein contain one or more asymmetric centers and thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

10 It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I is meant to include pharmaceutically acceptable salts.

 Compounds according to the invention are selective and potent inhibitors of PDE IV. The ability of the compounds to act in this way may be determined by the tests described in the Examples hereinafter.

15 The compounds according to the invention are thus of particular use in the prophylaxis and treatment of human diseases where an unwanted inflammatory response or muscular spasm (for example bladder or alimentary smooth muscle spasm) is present and where the elevation of cAMP levels may be expected to prevent or alleviate the inflammation and relax muscle.

20 Particular uses to which the compounds of the invention may be put include the prophylaxis and treatment of asthma, especially inflamed lung associated with asthma, cystic fibrosis, or in the treatment of inflammatory airway disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other benign and malignant proliferative skin diseases, endotoxic shock, septic shock, ulcerative colitis, Crohn's
25 disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, osteoporosis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult and infant respiratory distress syndrome, diabetes, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis and atherosclerosis.

30 Compounds of the invention also suppress neurogenic inflammation through elevation of cAMP in sensory neurons. They are, therefore, analgesic, antitussive and anti-hyperalgesic in inflammatory diseases associated with irritation and pain.

 Compounds of the invention also elevate cAMP in lymphocytes and thereby suppress unwanted lymphocyte activation in immune-based diseases such as

rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease.

Compounds of the invention also reduce gastric acid secretion and therefore can be used to treat conditions associated with hypersecretion of gastric acid.

5 Compounds of the invention suppress cytokine synthesis by inflammatory cells in response to immune or infectious stimulation. They are, therefore, useful in the treatment of bacterial, fungal or viral induced sepsis and septic shock in which cytokines such as tumour necrosis factor (TNF) are key mediators. Also compounds of the invention suppress inflammation and pyrexia due to cytokines
10 and are, therefore, useful in the treatment of inflammation and cytokine-mediated chronic tissue degeneration which occurs in diseases such as rheumatoid or osteoarthritis.

Over-production of cytokines such as TNF in bacterial, fungal or viral infections, or in diseases such as cancer, leads to cachexia and muscle wasting.

15 Compounds of the invention ameliorate these symptoms with a consequent enhancement of quality of life.

Compounds of the invention also elevate cAMP in certain areas of the brain and thereby counteract depression and memory impairment.

20 Compounds of the invention suppress cell proliferation in certain tumor cells and can be used, therefore, to prevent tumor growth and invasion of normal tissues.

For the prevention, prophylaxis or treatment of disease, the compounds may be administered to a mammalian patient in need of such prevention, prophylaxis or treatment, in an amount that is effective for preventing, controlling or treating the
25 disease. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

30 The compounds of Formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in the form of a pharmaceutical composition as described herein.

The term parenteral as used herein includes subcutaneous, intravenous, intramuscular or intrasternal injection or infusion techniques.

35 The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules,

5 syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, 10 corn starch or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or 15 glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for 20 example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are 25 suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxy-propylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of 30 ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous 35 suspensions may also contain one or more preservatives, for example ethyl, or n-

propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed

including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Examples of such materials include cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Combined therapy to

The compounds of formula I can also be used in combination with another active ingredient or ingredients. For example, for the treatment or prevention of inflammation, the present compounds may be used in conjunction with an antiinflammatory or analgesic agent such as an opiate agonist, a lipoxxygenase inhibitor, such as an inhibitor of 5-lipoxxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap and the like. Similarly, the instant compounds may be administered with a pain reliever; a potentiator such as caffeine, an H₂-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine such as loratidine.

Likewise, compounds of the present invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an

amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

Examples of other active ingredients that may be combined with a compound of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists such as those described in US 5,510,332, WO95/15973, WO96/01644, WO96/06108, WO96/20216, WO96/22966, WO96/31206, WO96/40781, WO97/03094, WO97/02289, WO 98/42656, WO98/53814, WO98/53817, WO98/53818, WO98/54207, and WO98/58902; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleminamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β 2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, piroprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acetmetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams

- (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) antagonists of the chemokine receptors, especially CCR-1, CCR-2, CCR-3, CXCR-3 and CCR-5; (i) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (j) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), α -glucosidase inhibitors (acarbose) and glitazones (troglitazone and pioglitazone); (k) preparations of interferon beta (interferon beta-1 α , interferon beta-1 β); (l) other compounds such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents.

- Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

- The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may contain from about 0.5 mg to about 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from as low as about 1 mg to as high as about 1500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg or 1000 mg.

- It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Methods of Synthesis

The compounds of Formula I of the present invention can be prepared according to the synthetic routes outlined in Schemes I to IV and by following the methods described herein.

5

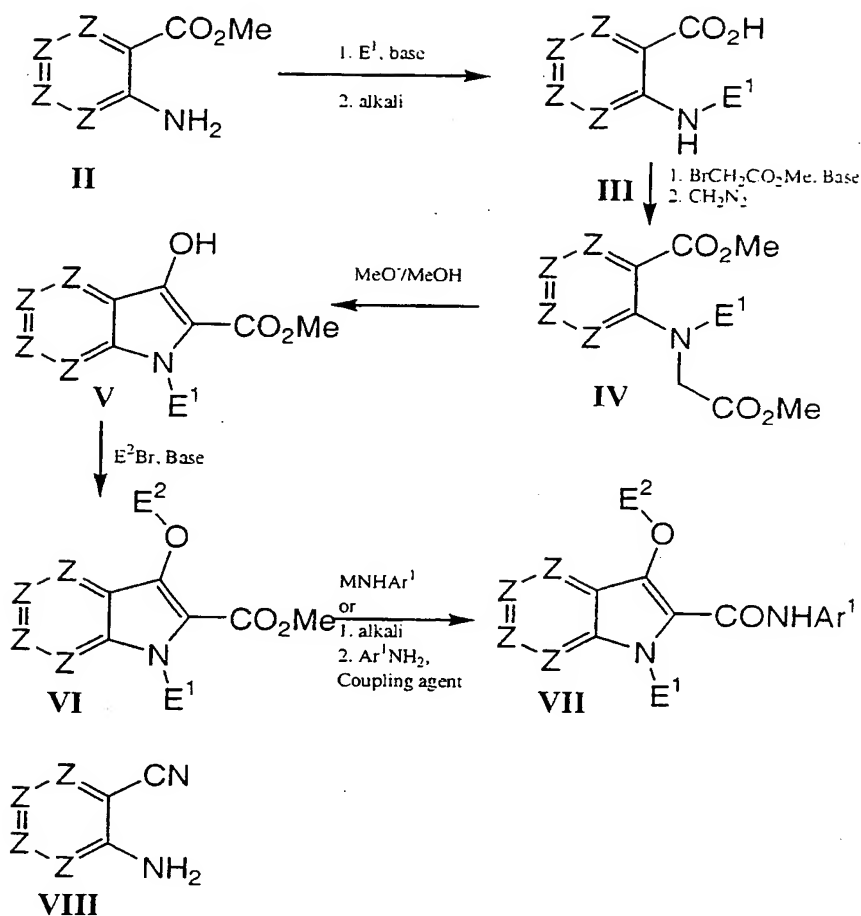
Scheme 1

Compounds of Formula I may be prepared by the method presented in Scheme 1 from an appropriately substituted anthranilic acid or Z = Nitrogen equivalent (II). Addition of an appropriate electrophile such as a E^1Br or E^1Cl (wherein E^1 represents $(CH_2)_d-Ar$ in the presence of a base, followed by alkaline saponification of the ester group leads to III. Reaction of III with methyl bromoacetate, followed by esterification with diazomethane yields IV. Reaction with methoxide in methanol leads to the cyclization product V. Alkylation of the indanol with the appropriate electrophile such as E^2Br (wherein E^2 represents $(CH_2)_b-X$ in the presence of a base and in a suitable solvent such as DMF gives VI. Reaction of VI with an alkaline metal (such as Li, Mg or Al) derivative of the appropriate NH_2-Ar^1 in a suitable solvent such as THF yields VII. Alternatively, VI can be first saponified with conditions such as alcoholic NaOH, and then reacted with the NH_2-Ar^1 in the presence of an amide coupling reagent such as DCC in an appropriate solvent to give VII.

20

Following the same sequence of events but starting with an anthranitrile or its Z = N equivalent (VII), one has access to the $X = CNR^4R^4$, $X = CNAr^1H$ and $X = CNR^4CH_2Ar^1$ series.

Scheme 1

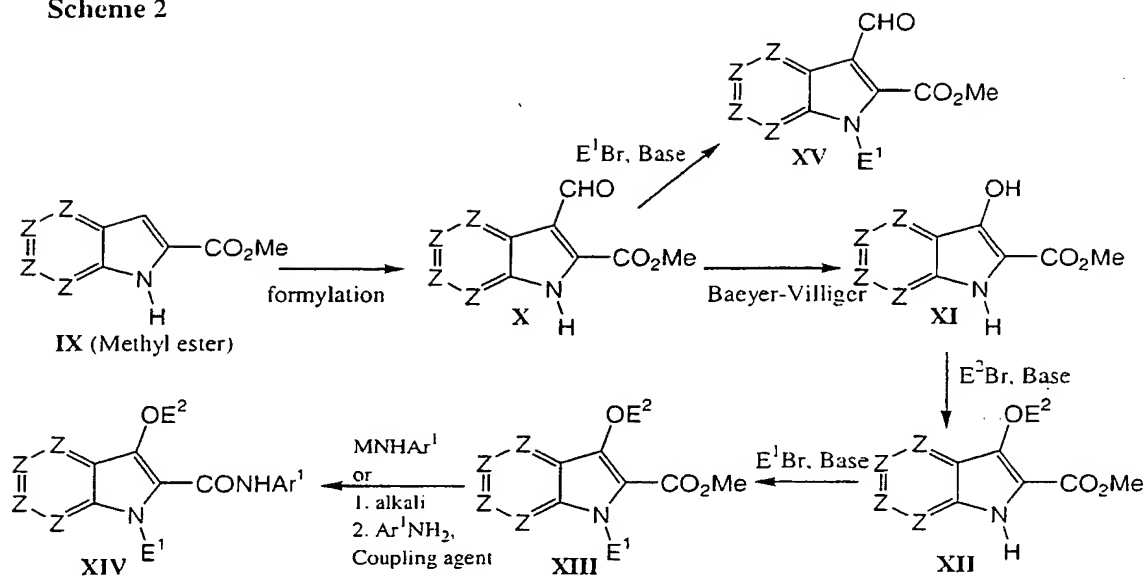


Scheme 2

- Compounds of Formula **I** may alternatively be prepared by the method presented in Scheme 2 from an appropriately substituted indole or Z = Nitrogen equivalent (**IX**). Formylation in Vilsmeier-Haack or similar conditions gives **X**, which in turn can be oxidized under Baeyer-Villiger conditions to give **XI**. Successive reactions with electrophiles such as bromides, chlorides or iodides in the presence of bases and in a polar solvent gives **XII**, and then **XIII**. The ester group of **XIII** is transformed in the amide as described above in Scheme 1.

Alternatively, the reaction with the E^1 electrophile may be conducted on **IX** to give **XV**, and the E^1 group carried through the same sequence to give the same product **XIV**.

Scheme 2



5

Scheme 3

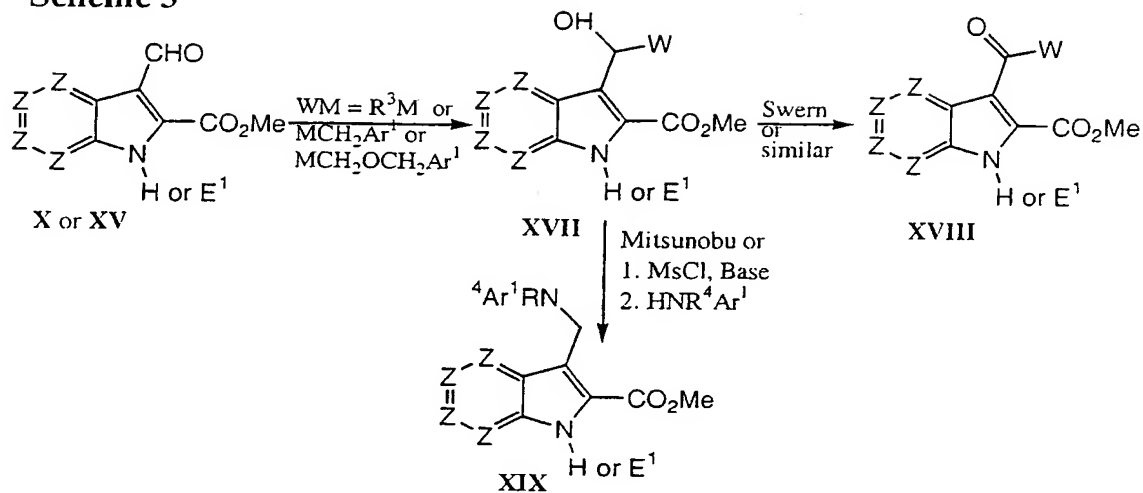
Compounds of Formula I may alternatively be prepared by the method presented in Scheme 3 from an appropriately substituted indole or Z = Nitrogen equivalent (X). Grignard or other organometallic reagents may be added to X or to the XVI to yield the alcohol XVII, which in turn can be oxidized to the ketone XVIII.

10 The rest of the sequence to compounds of Formula I is shown in Schemes 1 and 2.

In the case where W is H, with such reagents such as NaBH_4 , the resulting primary alcohol may further be transformed by a Mitsunobu type reaction to give XIX, which can undergo the rest of the sequence to give compounds of Formula I.

15

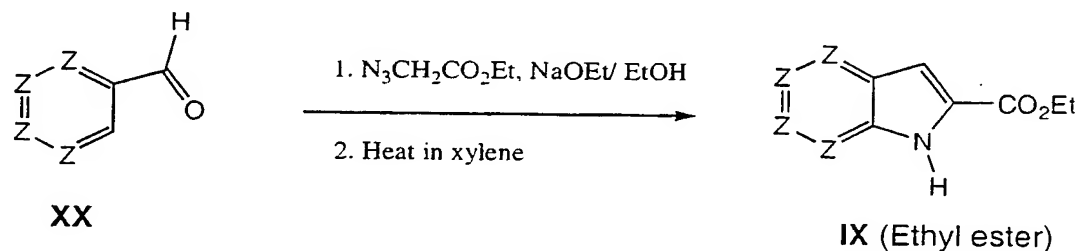
Scheme 3



Scheme 4

- Compounds of Formula **IX** may be prepared by the method presented in Scheme 4 from an appropriately substituted aldehyde (**XX**). Ethyl azidoacetate is condensed onto the aldehyde in a strong base such as ethoxide, and the resulting cinnamate is pyrolysed to yield the indole compound.

Scheme 4



Scheme 5

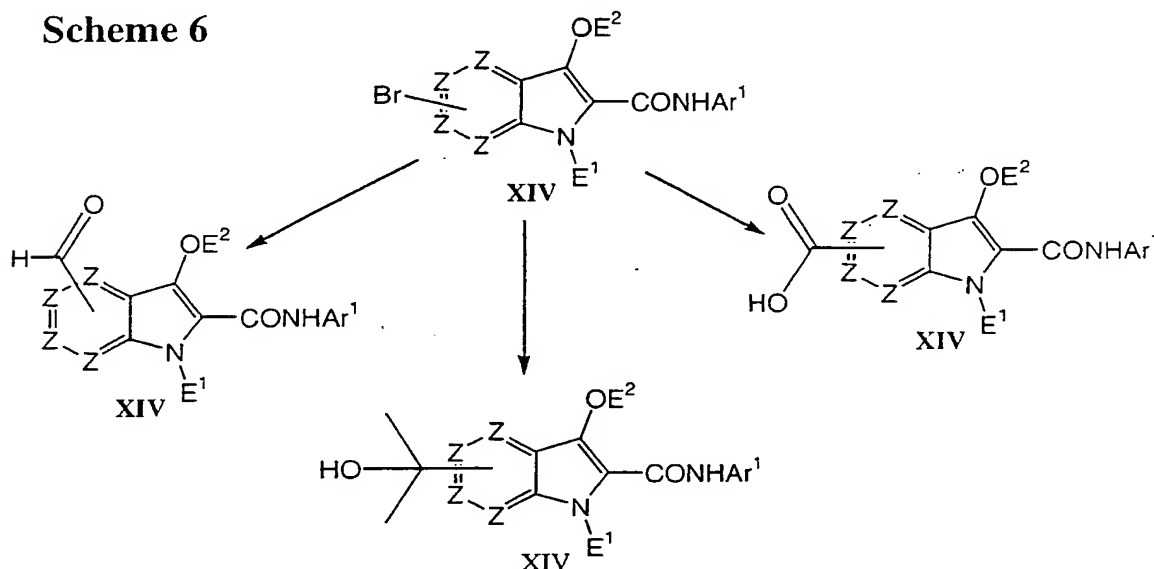
- Compounds of Formula **IX** may also be prepared by the method presented in Scheme 5 from an appropriately substituted methylated nitroaromatic (**XXI**). This compound is treated with a strong base such as ethoxide in ethanol, and condensed onto ethyl oxalate to give, after saponification, the pyruvic acid **XXII**. This acid is then esterified with diazomethane, for example, and then treated with a reagent such as iron in acetic acid to give the compound **IX** (Methyl ester).

Scheme 6

Compounds of formula I may be prepared by reaction of **XIV** first with a suitable metallation agent, such as n-BuLi, followed by trapping with an electrophile such as DMF to produce the aldehyde, acetone to produce the t-alcohol.

5 CO₂ to produce the carboxylic acid.

Scheme 6

Assays for Determining Biological Activity10 Measurement of whole-cell cAMP content

CHO-K1 cells were plated at a density of 10^6 cells/175 cm² containing complete media with 500 µg/ml hygromycin. The flasks were maintained in an incubator at 37°C with 5.0% CO₂ for 72 hr. The media was changed and the cells were allowed to grow overnight. The cells were washed and dissociated from the plate with PBS containing 0.5 mM EDTA. Cellular cAMP content was measured by

15 centrifuging the cell suspension at 150 g x 10 min. And resuspending the cells in a Hanks buffered salt solution at a density of 0.2×10^6 cells/ml. The cells were preincubated at room temperature for 15 min. and then incubated with 10 µM prostaglandin I₂ (PGI₂) and the indicated compound for an additional 10 min. Basal

20 cAMP levels were determined by incubating the cells in 0.1% DMSO. The incubations were terminated by the addition of HCl (0.1 N final) and the cells measured for cAMP as described below.

Determinations of whole-cell cAMP content were performed by incubating 100 µl reconstituted rabbit anti-succinyl cAMP serum with 100 µl of the whole-cell reaction or known cAMP standard and 30 pmol of ^{125}I -cAMP TME in a ScintiStripTM well (300 µl final volume) at room temperature for 18 h. Total cpm (B_0) was determined in the absence of sample of cAMP standard. The reaction mixture was then aspirated out of the well, and the individual wells were counted in a Beckman LS 6000SC with the window open from 10-999 for 1 min. The data were expressed as $\%B/B_0 = [(\text{standard or sample cpm} - \text{non-specific cpm}) / (B_0 \text{ cpm} - \text{non-specific cpm})] \times 100$. Non-specific cpm were determined by incubating only the ^{125}I -cAMP TME with assay buffer (50 mM acetate; pH 5.8) in the ScintiStripTM well. All determinations were performed in triplicate.

Phosphodiesterase Scintillation Proximity Assay

CHO-K1 cells were lysed by sonication for 10 secs at a power setting of 50% (Braunsonic Model 2000) in an ice cold solution containing 50 mM Tris, pH 7.5; 1mM EDTA; and 200 µM β-mercaptoethanol. The soluble and particulate fractions of the cell were obtained by centrifuging the sonicate for 90 min. at 100,000 x g at 4°C. PDE activity was measured in a solution containing 50 mM Tris, pH 7.5; 10mM MgCl₂; 1 mM EDTA; and 100 nM (or indicated) ^3H -cAMP (100 µl final volume) in the presence of varying concentrations of inhibitor. The reaction mixture containing enzyme was incubated for 10 min. at 30°C in 96-well View Plates (Packard), and terminated by the addition of 50 µl Phosphodiesterase Scintillation Proximity Assay (SPA) Beads (Amersham) containing 18 mM ZnSO₄. The amount of ^3H -cAMP hydrolysis was determined by counting the plates in a Wallac 1450 µBeta LSC counter.

The Elevation of cAMP in Leukocytes

The effect of compounds of the invention on intracellular cAMP was investigated using human neutrophils or guinea pig eosinophils. Human neutrophils were separated from peripheral blood, incubated with dihydrocytochalasin B and the test compound for 10 min and then stimulated with FMLP. Guinea pig eosinophils were harvested by peritoneal lavage of animals previously treated with intra-peritoneal injections of human serum. Eosinophils were separated from the peritoneal exudate and incubated with isoprenaline and test compound. With both cell types, suspensions

were centrifuged at the end of the incubation, the cell pellets were resuspended in buffer and boiled for 10 min prior to measurement of cAMP by specific radioimmunoassay (DuPont).

- 5 The most potent compounds according to the Examples induced a concentration-dependent elevation of cAMP in neutrophils and/or eosinophils at concentrations of 0.1nM to 1µM.

Anti-allergic Activity in vivo

- 10 Compounds of the invention were tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitised guinea pigs. Guinea pigs were initially sensitised to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of antigen in combinations with aluminium hydroxide and pertussis vaccine. Booster doses of antigen were given two and four weeks later and at six weeks, animals were
- 15 challenged with aerosolised ovalbumin whilst under cover of an intraperitoneally administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also removed for histological examination for inflammatory damage. Administration of compounds of
- 20 the Examples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with compounds of the Examples.

SPA based PDE activity assay protocol

25 Compounds which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in 96-well plate format as follows:

- 30 In a 96 well-plate at 30°C was added the test compound (dissolved in 2 µl DMSO), 188 µl of substrate buffer containing [2,8-³H] adenosine 3',5'-cyclic phosphate (cAMP, 100 nM to 50 µM), 10 mM MgCl₂, 1 mM EDTA, 50 mM Tris, pH 7.5. The reaction was initiated by the addition of 10 µl of human recombinant PDE-IV (the amount was controlled so that ~ 10% product was formed in 10 min. at 30°C). The reaction was stopped after 10 min. by the addition of 1 mg of PDE-SPA

beads (Amersham). The product AMP generated was quantified on a Microbeta 96-well plate counter. The signal in the absence of enzyme was defined as the background. 100% activity was defined as the signal detected in the presence of enzyme and DMSO with the background subtracted. Percentage of inhibition was calculated accordingly. IC₅₀ value was approximated with a non-linear regression fit of the standard 4-parameter/multiple binding sites equation from a ten point titration.

LPS and fMLP-Induced TNF- α and LTB₄ Assays in Human Whole Blood

Whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as PDE IV-selective inhibitors. Normal non-stimulated human blood does not contain detectable levels of TNF- α and LTB₄. Upon stimulation with LPS, activated monocytes express and secrete TNF- α up to 8 hours and plasma levels remain stable for 24 hours. Published studies have shown that inhibition of TNF- α by increasing intracellular cAMP via PDE IV inhibition and/or enhanced adenylyl cyclase activity occurs at the transcriptional level. LTB₄ synthesis is also sensitive to levels of intracellular cAMP and can be completely inhibited by PDE IV-selective inhibitors. As there is little LTB₄ produced during a 24 hour LPS stimulation of whole blood, an additional LPS stimulation followed by fMLP challenge of human whole blood is necessary for LTB₄ synthesis by activated neutrophils. Thus, using the same blood sample it is possible to evaluate the potency of a compound on two surrogate markers of PDE IV activity in the whole blood.

Fresh blood was collected in heparinized tubes by venipuncture from healthy human volunteers (male and female). These subjects had no apparent inflammatory conditions and had not taken any NSAIDs for at least 4 days prior to blood collection. Five hundred μ L aliquots of blood were pre-incubated with either 2 μ L of vehicle (DMSO) or 2 μ L test compound at varying concentrations for 15 minutes at 37°C. This was followed by the addition of either 10 μ L vehicle (PBS) as blanks or 10 μ L LPS (1 μ g/ml final concentration, Sigma Chem, #L-2630 from *E. coli*, serotype 0111:B4; diluted in 0.1% w/v BSA (in PBS)). After 24 hours of incubation at 37°C, another 10 μ L of PBS (blank) or 10 μ L of LPS (1 μ g/ml final concentration) was added to blood and incubated for 30 minutes at 37°C. The blood was then challenged with either 10 μ L of PBS (blank) or 10 μ L of fMLP (1 μ M final concentration, Sigma Chem #F-3506; diluted in 1% w/v BSA (in PBS)) for 15 minutes at 37°C. The blood samples were centrifuged at 1500xg for 10 minutes at

- 4°C to obtain plasma. A 50µL aliquot of plasma was mixed with 200µL methanol for protein precipitation and centrifuged as above. The supernatant was assayed for LTB₄ using an enzyme immunoassay kit (Cayman Chemicals #520111) according to the manufacturer's procedure. TNF-α was assayed in diluted plasma (in PBS) using an
- 5 ELISA kit (Cistron Biotechnology) according to manufacturer's procedure.

Assays for Determining Biological Activity

Measurement of whole-cell cAMP content

- CHO-K1 cells were plated at a density of 10^6 cells/175 cm² containing
- 10 complete media with 500 µg/ml hygromycin. The flasks were maintained in an incubator at 37°C with 5.0% CO₂ for 72 hr. The media was changed and the cells were allowed to grow overnight. The cells were washed and dissociated from the plate with PBS containing 0.5 mM EDTA. Cellular cAMP content was measured by centrifuging the cell suspension at 150 g x 10 min. And resuspending the cells in a
- 15 Hanks buffered salt solution at a density of 0.2×10^6 cells/ml. The cells were preincubated at room temperature for 15 min. and then incubated with 10 µM prostaglandin I₂ (PGI₂) and the indicated compound for an additional 10 min. Basal cAMP levels were determined by incubating the cells in 0.1% DMSO. The incubations were terminated by the addition of HCl (0.1 N final) and the cells
- 20 measured for cAMP as described below.

- Determinations of whole-cell cAMP content were performed by incubating 100 µl reconstituted rabbit anti-succinyl cAMP serum with 100 µl of the whole-cell reaction or known cAMP standard and 30 pmol of ¹²⁵I-cAMP TME in a ScintiStripTM well (300 µl final volume) at room temperature for 18 h. Total cpm
- 25 (B₀) was determined in the absence of sample of cAMP standard. The reaction mixture was then aspirated out of the well, and the individual wells were counted in a Beckman LS 6000SC with the window open from 10-999 for 1 min. The data were expressed as %B/B₀ = [(standard or sample cpm - non-specific cpm) / (B₀ cpm - non-specific cpm)] x 100. Non-specific cpm were determined by incubating only the ¹²⁵I-
- 30 cAMP TME with assay buffer (50 mM acetate; pH 5.8) in the ScintiStripTM well. All determinations were performed in triplicate.

Phosphodiesterase Scintillation Proximity Assay

CHO-K1 cells were lysed by sonication for 10 secs at a power setting of 50% (Braunsonic Model 2000) in an ice cold solution containing 50 mM Tris, pH 7.5; 1mM EDTA; and 200 μ M β -mercaptoethanol. The soluble and particulate fractions of the cell were obtained by centrifuging the sonicate for 90 min. at 100,000 x g at 4°C. PDE activity was measured in a solution containing 50 mM Tris, pH 7.5; 10mM MgCl₂; 1 mM EDTA; and 100 nM (or indicated) ³H-cAMP (100 μ l final volume) in the presence of varying concentrations of inhibitor. The reaction mixture containing enzyme was incubated for 10 min. at 30°C in 96-well View Plates (Packard), and terminated by the addition of 50 μ l Phosphodiesterase Scintillation Proximity Assay (SPA) Beads (Amersham) containing 18 mM ZnSO₄. The amount of ³H-cAMP hydrolysis was determined by counting the plates in a Wallac 1450 μ Beta LSC counter.

The Elevation of cAMP in Leukocytes

The effect of compounds of the invention on intracellular cAMP was investigated using human neutrophils or guinea pig eosinophils. Human neutrophils were separated from peripheral blood, incubated with dihydrocytochalasin B and the test compound for 10 min and then stimulated with FMLP. Guinea pig eosinophils were harvested by peritoneal lavage of animals previously treated with intra-peritoneal injections of human serum. Eosinophils were separated from the peritoneal exudate and incubated with isoprenaline and test compound. With both cell types, suspensions were centrifuged at the end of the incubation, the cell pellets were resuspended in buffer and boiled for 10 min prior to measurement of cAMP by specific radioimmunoassay (DuPont).

The most potent compounds according to the Examples induced a concentration-dependent elevation of cAMP in neutrophils and/or eosinophils at concentrations of 0.1nM to 1 μ M.

Anti-allergic Activity in vivo

Compounds of the invention were tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitised guinea pigs. Guinea pigs were initially sensitised to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of

antigen in combinations with aluminium hydroxide and pertussis vaccine. Booster doses of antigen were given two and four weeks later and at six weeks, animals were challenged with aerosolised ovalbumin whilst under cover of an intraperitoneally administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also removed for histological examination for inflammatory damage. Administration of compounds of the Examples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with compounds of the Examples.

SPA based PDE activity assay protocol

Compounds which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in 96-well plate format as follows:

In a 96 well-plate at 30°C was added the test compound (dissolved in 2 µl DMSO), 188 µl of substrate buffer containing [2,8-³H] adenosine 3',5'-cyclic phosphate (cAMP, 100 nM to 50 µM), 10 mM MgCl₂, 1 mM EDTA, 50 mM Tris, pH 7.5. The reaction was initiated by the addition of 10 µl of human recombinant PDE-IV (the amount was controlled so that ~ 10% product was formed in 10 min. at 30 °C). The reaction was stopped after 10 min. by the addition of 1 mg of PDE-SPA beads (Amersham). The product AMP generated was quantified on a Microbeta 96-well plate counter. The signal in the absence of enzyme was defined as the background. 100% activity was defined as the signal detected in the presence of enzyme and DMSO with the background subtracted. Percentage of inhibition was calculated accordingly. IC₅₀ value was approximated with a non-linear regression fit of the standard 4-parameter/multiple binding sites equation from a ten point titration.

LPS and fMLP-Induced TNF-α and LTB₄ Assays in Human Whole Blood

Whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as PDE IV-selective inhibitors. Normal non-stimulated human blood does not contain detectable levels of TNF-α and LTB₄. Upon stimulation with LPS, activated monocytes express

and secrete TNF- α up to 8 hours and plasma levels remain stable for 24 hours. Published studies have shown that inhibition of TNF- α by increasing intracellular cAMP via PDE IV inhibition and/or enhanced adenylyl cyclase activity occurs at the transcriptional level. LTB₄ synthesis is also sensitive to levels of intracellular cAMP and can be completely inhibited by PDE IV-selective inhibitors. As there is little LTB₄ produced during a 24 hour LPS stimulation of whole blood, an additional LPS stimulation followed by fMLP challenge of human whole blood is necessary for LTB₄ synthesis by activated neutrophils. Thus, using the same blood sample it is possible to evaluate the potency of a compound on two surrogate markers of PDE IV activity in the whole blood.

Fresh blood was collected in heparinized tubes by venipuncture from healthy human volunteers (male and female). These subjects had no apparent inflammatory conditions and had not taken any NSAIDs for at least 4 days prior to blood collection. Five hundred μ L aliquots of blood were pre-incubated with either 2 μ L of vehicle (DMSO) or 2 μ L test compound at varying concentrations for 15 minutes at 37°C. This was followed by the addition of either 10 μ L vehicle (PBS) as blanks or 10 μ L LPS (1 μ g/ml final concentration, Sigma Chem, #L-2630 from *E. coli*, serotype 0111:B4; diluted in 0.1% w/v BSA (in PBS)). After 24 hours of incubation at 37°C, another 10 μ L of PBS (blank) or 10 μ L of LPS (1 μ g/ml final concentration) was added to blood and incubated for 30 minutes at 37°C. The blood was then challenged with either 10 μ L of PBS (blank) or 10 μ L of fMLP (1 μ M final concentration, Sigma Chem #F-3506; diluted in 1% w/v BSA (in PBS)) for 15 minutes at 37°C. The blood samples were centrifuged at 1500xg for 10 minutes at 4°C to obtain plasma. A 50 μ L aliquot of plasma was mixed with 200 μ L methanol for protein precipitation and centrifuged as above. The supernatant was assayed for LTB₄ using an enzyme immunoassay kit (Cayman Chemicals #520111) according to the manufacturer's procedure. TNF- α was assayed in diluted plasma (in PBS) using an ELISA kit (Cistron Biotechnology) according to manufacturer's procedure.

30

EXAMPLES

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:

1. All the end products of the formula I were analyzed by NMR, TLC and elementary analysis or mass spectroscopy.

2. Intermediates were analyzed by NMR and TLC.
3. Most compounds were purified by flash chromatography on silica gel, recrystallization and/or swish (suspension in a solvent followed by filtration of the solid).
- 5 4. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only.

The following intermediates were prepared according to literature procedures, or purchased from the following vendor:

- 10 1. 4-Bromo-2-nitro-phenylpyruvic acid: Kosuge, T.; Ishida, H.; Inaba, A.; Nukaya, H. *Chem. Pharm. Bull.* **1985**, *33*, 1414-1419.
2. Ethyl 3-aminoindole-2-carboxylate: Unangst, P. C. *J. Heterocyclic Chem.* **1983**, *20*, 495-499.
3. Ethyl 5-bromoindole-2-carboxylate: BIOSYNTH AG.
- 15 4. Lithium 3-pyridylamide has been prepared such as lithium *N*-isopropylcyclohexylamide : Paquette, L. A.; Ewing, G. D. *J. Org. Chem.* **1975**, *40*, 2965-2966.

EXAMPLE 1

20 {1-[(4-FLUOROPHENYL)METHYL]-3-(PHENYLMETHOXY)INDOL-2-YL}-*N*-
(3-PYRIDYL)FORMAMIDE (COMPOUND 173)

Step 1: Methyl 2-{[(4-fluorophenyl)methyl]amino}benzoate

A suspension of 77 g of potassium carbonate in a mixture of 100 mL of methyl ethyl ketone, 50 g of 4-fluorobenzyl bromide and 26 mL of the methyl 2-aminobenzoate was refluxed for 8h, cooled to room temperature, filtered and concentrated. Filtration on 600 mL of silica gel and washing with 10% ethyl acetate in hexane afforded the desired material as a yellow oil (41 g, 85% purity). This material was used as such for the next step.

30 Step 2: Methyl 1-[(4-fluorophenyl)methyl]-3-hydroxyindole-2-carboxylate

A solution of the previous ester (36 g) in 90 mL of MeOH, 27 mL of 10N aqueous NaOH and 225 mL of THF was refluxed for 2 h. The reaction mixture was poured into 550 mL of 1N HCl and extracted three times with ethyl acetate. The organic phase was washed with brine and dried over MgSO₄. After evaporation, the solid was swished in 10% ether in hexane.

This solid was then combined with 28 mL of methyl bromoacetate and 37 g of K₂CO₃, in solution in 225 mL of MeOH and 450 mL H₂O. The mixture was refluxed for 18 h. The cooled reaction mixture was poured onto 65 mL of concentrated HCl in 700 mL of ice, and extracted with ethyl acetate. The organic extracts were dried over MgSO₄, titrated with an ether solution of CH₂N₂ and the solvents were evaporated under vacuum to give the crude diester.

This crude diester was dissolved in 450 mL of MeOH containing 20 g of sodium methoxide, and refluxed for 30 min. This mixture is then cooled and acidified with 2N HCl and extracted with ethyl acetate. The organic phase was dried over MgSO₄ and evaporated to dryness. The solid is swished in 200 mL of 5% ethyl acetate in hexane to give the title compound as a white solid.

¹H NMR (acetone-d₆) δ 3.91 (s, 3H), 5.69 (s, 2H), 7.04 (t, 2H), 7.10 (m, 3H), 7.37 (t, 1H), 7.51 (d, 1H), 7.72 (d, 1H), 8.7 (s, 1H).

20 Step 3: 1-[(4-Fluorophenyl)methyl]-3-(phenylmethoxy)indole-2-carboxylic acid

To a solution 5.3 g of the previous ester and 2.53 mL of benzyl bromide in 17 mL of methyl ethyl ketone was added 3.18 g of K₂CO₃. The mixture was refluxed for 2 h and then cooled to room temperature. It was then filtered, the solids were washed with toluene and the combined liquid phases evaporated. Flash chromatography (toluene) yielded the methyl ester of the title compound as an orange solid. This ester was dissolved in 23 mL of ethanol and 5 mL water, and 2.3 mL of 10N NaOH was added. The mixture was heated for 40 min at 90°C and then cooled. Acidification with 1N HCl and extraction with ethyl acetate yielded, after evaporation, an off-white solid.

^1H NMR (CDCl_3) δ 5.48 (s, 2H), 5.75 (s, 2H), 6.93 (t, 2H), 7.02 (t, 2H), 7.16 (m, 1H), 7.39 (m, 7H), 7.76 (d, 1H).

5 Step 4: { 1-[(4-Fluorophenyl)methyl]-3-(phenylmethoxy) indol-2-yl }-N-(3-pyridyl) formamide

Into a dry 25 mL round bottom flask was placed 1-[(4-fluorophenyl)methyl]-3-(phenylmethoxy) indole-2-carboxylic acid (50 mg) along with benzene (2.0 mL), *i*-Pr₂NEt (0.2 mL) followed by SOCl₂ (20 μ L) and allowed to stir at room temperature for 0.5 hours. To the resulting mixture was then added 3-aminopyridine (20 mg) and stirred for an additional 4 hours. At this time, the reaction mixture was poured into a separatory funnel containing 25 mL H₂O/ 25 mL EtOAc, the layers were separated and the aqueous layer was extracted with EtOAc (2x25 mL). The combined organic layers were dried over anhydrous MgSO₄, concentrated and the resulting material was purified by flash chromatography eluting with 50% EtOAc/hexanes to provide the title amide (14.1 mg) as a light yellow solid.

^1H NMR (CDCl_3) δ 5.45 (s, 2H), 5.90 (s, 2H), 6.92 (m, 2H), 7.08 (m, 2H), 7.20 (m, 2H), 7.40 (m, 7H), 7.82 (m, 1H), 8.02 (m, 1H), 8.04 (s, 1H), 8.28 (s, 1H), 9.55 (s, 1H). MS (+APCI) m/z 452.2 (M+H)⁺

20

EXAMPLE 2

{ 1-[(4-FLUOROPHENYL)METHYL]-3-(PHENYLMETHOXY)INDOL-2-YL }-N-[3-(METHYLSULFONYL) PHENYL] FORMAMIDE (COMPOUND 147)

Into a dry 50 mL round bottom flask was placed 1-[(4-fluorophenyl)methyl]-3-(phenylmethoxy) indole-2-carboxylic acid (50 mg) along with dry THF (5.0 mL), *i*-Pr₂NEt (0.1 mL), cooled to 0 °C, added MsCl (10 μ L) and allowed to stir for 0.5 hours. To this cold stirred solution 3-(methylsulfonyl)aniline (65 mg) was added and allowed to stir at room temperature for 2 hours. The resulting reaction mixture was poured into a separatory funnel containing 50 mL H₂O/ 50 mL EtOAc, the layers were separated, the aqueous layer was extracted with EtOAc (2x50 mL), the combined organic layers were washed with brine, dried over anhydrous

MgSO₄ and concentrated. The resulting material was further purified by flash chromatography eluting with 50% EtOAc/hexanes to provide 42.4 mg of the title amide as an off-white solid.

¹H NMR (acetone-d₆) δ 3.10 (s, 2H), 5.59 (s, 2H), 5.96 (s, 2H), 7.00 (m, 2H),
5 7.17 (m, 3H), 7.43 (m, 4H), 7.56 (m, 6H), 7.98 (d, 1H), 8.27 (m, 1H), 9.82 (s, 1H).

EXAMPLE 3

{1-[(4-FLUOROPHENYL)METHYL]-3-(PHENYLMETHOXY) INDOL-2-YL}-N-
(3-PYRIDYLMETHYL) FORMAMIDE (COMPOUND 185)

10 Following the procedure describing the preparation of example 166, 1-
[(4-fluorophenyl)methyl]-3-(phenylmethoxy) indole-2-carboxylic acid (50 mg) in
THF (3.0 mL) at 0° C was treated with *i*-Pr₂NEt (0.1 mL), MsCl (10 μL), stirred for
0.5 hours and then added 3-(aminomethyl)pyridine (20 mg). After work-up and
purification by flash chromatography eluting with 30% EtOAc/hexanes the title amide
15 (27.4 mg) was isolated as a light yellow oil.

¹H NMR (acetone-d₆) δ 4.52 (d, 2H), 5.37 (s, 2H), 6.97 (m, 2H), 7.07
(m, 3H), 7.30 (m, 7H), 7.58 (m, 1H), 7.61 (m, 1H), 7.82 (m, 1H), 8.18 (m, 1H), 8.46
(m, 1H), 8.54 (m, 1H). MS (+APCI) *m/z* 466.4 (M+H)⁺.

20

EXAMPLE 4

{1-[(4-FLUOROPHENYL)METHYL]-3-(PHENYLMETHOXY) INDOL-2-YL}-N-
(4-PYRIDYLMETHYL) FORMAMIDE (COMPOUND 186)

Following the procedure describing the preparation of example 166, 1-[(4-
fluorophenyl)methyl]-3-(phenylmethoxy) indole-2-carboxylic acid (50 mg) in THF
25 (5.0 mL) at 0 °C was treated with *i*-Pr₂NEt (0.1 mL), MsCl (10 μL) and after 0.5 hours
4-aminomethylpyridine (20 mg) was added to the reaction mixture. After work-up
and purification by flash chromatography eluting with 20% EtOAc/hexanes the title
amide (15 mg) was obtained as a light yellow oil.

^1H NMR (acetone- d_6) δ 4.50 (m, 2H), 5.46 (s, 2H), 5.95 (s, 2H), 7.00 (m, 2H), 7.16 (m, 5H), 7.35 (m, 4H), 7.40 (m, 2H), 7.52 (m, 1H), 7.85 (m, 1H), 8.16 (m, 1H), 8.46 (m, 2H).

5

EXAMPLE 5

METHY 4-{[3-(PHENYLMETHOXY)-2-(N-(3-PYRIDYL)CARBAMOYL METHYL) BENZOATE (COMPOUND 142)]

Into a 100 mL round bottom flask was placed methyl 3-(phenylmethoxy)indole-2-carboxylate (1.0 g) along with THF (20 mL). To this stirred solution at room temperature was added lithium 3-pyridylamide (0.3 M in THF) until TLC indicated the consumption of starting material. The resulting reaction mixture was poured into a separatory funnel containing 50 mL H_2O / 100 mL EtOAc, the layers were separated and the organic layer was washed with a 5% aqueous AcOH solution (2x50 mL). The organic layer was washed with brine, dried over anhydrous MgSO_4 , concentrated and the residue was purified by flash chromatography eluting with 50% EtOAc/hexanes to provide 550 mg of the corresponding amide. To a flask containing the above amide (300 mg) in DMF (5.0 mL) at 0 °C was added 80 mg of a NaH suspension (60% in oil) and allowed to stir at room temperature for 0.5 hours. To this mixture was then added methyl 4-(bromomethyl)benzoate (225 mg) and the reaction was allowed to stir at room temperature overnight. At this time, the reaction mixture was poured into a separatory funnel containing 50 mL H_2O / 50 mL EtOAc, the layers were separated and the aqueous layer was extracted with EtOAc (2x25 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , concentrated and purified by flash chromatography eluting with 30% EtOAc/hexanes. The title amide (175 mg) was obtained as an off-white solid.

^1H NMR (acetone- d_6) δ 3.82 (s, 3H), 5.62 (s, 2H), 6.06 (s, 2H), 7.23 (m, 4H), 7.36 (m, 4H), 7.55 (m, 3H), 7.90 (m, 2H), 7.98 (m, 2H), 8.42 (m, 1H), 8.46 (d, 1H), 9.66 (s, 1H). MS (+APCI) m/z 492.4 (M+H) $^+$.

30

EXAMPLE 6

(1-{{[4-(1-HYDROXY-ISOPROPYL)PHENYL]METHYL}-3-(PHENYLMETHOXY)
INDOL-2-YL}-N-(3-PYRIDYL) FORMAMIDE (COMPOUND 136)

Into a 50 mL round bottom flask was placed the above benzoate (example 5) (100 mg) along with THF (10 mL) and, to this stirred solution, was added MeMgCl (0.4 mL, 3.0 M solution in THF) and allowed to stir at room temperature for four hours. At this time, the reaction mixture was quenched by the addition of 10 mL of a saturated aqueous NH₄Cl solution and this mixture was poured into a separatory funnel containing 50 mL H₂O/ 50 mL EtOAc. The layers were separated, the aqueous layer was extracted with EtOAc (50 mL) and the combined organic layers were washed with brine, dried over anhydrous MgSO₄ and concentrated. The collected material was further purified by flash chromatography eluting with 50% EtOAc/hexanes to provide the title alcohol (30 mg) as a light yellow solid.

¹H NMR (acetone-d₆) δ 1.42 (s, 6H), 5.60 (s, 2H), 5.97 (s, 2H), 7.05 (d, 2H), 7.18 (m, 1H), 7.25 (m, 1H), 7.57 (m, 3H), 7.97 (m, 2H), 8.24 (m, 1H), 8.49 (d, 1H), 9.67 (s, 1H). MS (+APCI) m/z 492.5 (M+H)⁺.

EXAMPLE 7

{1-[(4-METHYLPHENYL)METHYL]-3-(PHENYLMETHOXY) INDOL-2-YL}-N-
(3-PYRIDYL) FORMAMIDE (COMPOUND 73)

Following the procedure describing the preparation of example 6, methyl 3-(phenylmethoxy)indole-2-carboxylate (100 mg) in DMF (5.0 mL) was treated with 12 mg of a NaH suspension (60% in oil) followed by 4-methylbenzyl bromide (100 mL). After work-up the crude alkylated material was taken up in dry THF (10 mL) and treated with the lithium 3-pyridylamide (0.3 M in THF) solution as described previously. Following work-up and purification by flash chromatography the title indole (58.7 mg) was obtained as a white solid.

¹H NMR (acetone-d₆) δ 2.22 (s, 3H), 5.59 (s, 2H), 5.94 (s, 2H), 7.01 (m, 4H), 7.16 (m, 1H), 7.25 (m, 1H), 7.38 (m, 1H), 7.53 (m, 3H), 7.99 (m, 2H), 8.23 (m, 1H), 8.49 (d, 1H), 9.65 (s, 1H).

EXAMPLE 8

(1-{[4-(*TERT*-BUTYL)PHENYL]METHYL}-3-(PHENYLMETHOXY) INDOL-2-YL)-*N*-(3-PYRIDYL) FORMAMIDE (COMPOUND 172)

Into a round bottom flask was placed methyl 3-(phenylmethoxy)indole-2-carboxylate (50 mg) along with DMF (1.0 mL), THF (1.0 mL) and 10 mg of a NaH suspension (60% in oil). To this stirred mixture was added 4-*tert*-butylbenzyl bromide and allowed to stir at room temperature overnight. At this time, the reaction mixture was diluted with H₂O, poured into a teflon fritted cartridge and extracted with CH₂Cl₂. The filtrate was concentrated and then treated with THF/H₂O (5.0 mL, 1:1), MeOH (2.0 mL), NaOH (1 mL of a 1N aq. solution) and allowed to stir at room temperature overnight. At this time, the reaction mixture was acidified to pH 4 with an aqueous 1N HCl solution, diluted with 2 mL H₂O, extracted with CH₂Cl₂ through a teflon fritted cartridge as above and the filtrate was concentrated. The resulting crude carboxylic acid was taken up in THF (2.0 mL) and treated with *i*-Pr₂NEt (0.1 mL), MsCl (10 µL) followed by 3-aminopyridine (50 mg) as described previously for the preparation of example 166. After work-up and purification by flash chromatography 10.6 mg of the title amide was isolated.

¹H NMR (acetone-d₆) δ 1.22 (s, 9H), 5.59 (s, 2H), 5.96 (s, 2H), 7.05 (m, 2H), 7.17 (m, 1H), 7.32 (m, 7H), 7.57 (m, 3H), 7.97 (m, 2H), 8.24 (m, 1H), 8.49 (d, 1H), 9.68 (s, 1H). MS (+APCI) m/z 490.6 (M+H)⁺.

EXAMPLE 9

(1-{[4-(TRIFLUORMETHYL)PHENYL]METHYL}-3-(PHENYL METHOXY)INDOL-2-YL)-*N*-(3-PYRIDYL) FORMAMIDE (COMPOUND 148)

Following the experimental procedure describing the preparation of example 193, 9.8 mg of the title amide was isolated.

¹H NMR (acetone-d₆) δ 5.63 (s, 2H), 6.08 (s, 2H), 7.24 (m, 4H), 7.36 (m, 4H), 7.57 (m, 5H), 7.97 (m, 1H), 8.23 (d, 1H), 8.25 (d, 1H), 8.46 (d, 1H), 9.67 (s, 1H). MS (+APCI) m/z 502.4 (M+H)⁺.

EXAMPLE 10

(1-{{[4-(DIFLUOROMETHOXY)PHENYL]METHYL}-3-(PHENYL
METHOXY)INDOL-2-YL)-N-(3-PYRIDYL) FORMAMIDE (COMPOUND 16)

Following the general procedure describing the preparation of example
5 8, 3-(phenylmethoxy)indole-2-carboxylate (100 mg) in DMF (2.0 mL) was treated
with 10 mg of a NaH suspension (60% in oil) followed by 4-(difluoromethoxy)benzyl
bromide (120 mL). After work-up the crude alkylated material was taken up in THF
(5.0 mL) and treated with excess lithium 3-pyridylamide (0.3 M in THF). Following
the usual work-up and purification as described previously, the title amide (50.6 mg)
10 was obtained as a white solid.

¹H NMR (acetone-d₆) δ 5.59 (s, 2H), 5.96 (s, 2H), 7.06-6.70 (m, 3H),
7.17 (m, 3H), 7.25 (m, 1H), 7.35 (m, 4H), 7.55 (m, 3H), 7.96 (m, 2H), 8.24 (m, 1H),
8.48 (d, 1H), 9.66 (s, 1H). MS (+APCI) m/z 500.5 (M+H)⁺.

15

EXAMPLE 11

{3-(CYCLOPROPYLMETHOXY)-1-[(4-FLUOROPHENYL)METHYL]INDOL-2-
YL)-N-(3-PYRIDYL)FORMAMIDE (COMPOUND 154)

Step 1: {1-[(4-Fluorophenyl)methyl]-3-methoxyindol-2-yl}-N-(3-pyridyl)formamide

A solution containing 102 mg of methyl 1-[(4-fluorophenyl)methyl]-3-
20 hydroxyindole-2-carboxylate, 74 mg of MeOH and 152 mg of di-*tert*-butyl
azodicarboxylate in 1.2 mL of THF and 0.6 mL of CH₂Cl₂ was treated dropwise with
a solution containing 171 mg of triphenylphosphine in 0.6 mL of CH₂Cl₂. The
resulting reaction mixture was stirred overnight at room temperature. The organic
solvents were removed under vacuum and the crude mixture was treated with 11 mL
25 of a solution of lithium 3-pyridylamide (0.3 M in THF). The organic solvents were
removed under vacuum, CH₂Cl₂ was added and the organic phase was washed 3 times
with aqueous acetic acid (0.05 M). The desired material was extracted with a
cartridge filled with 500 mg of sulphonic acid resin (Varian SCX). The resin was
washed with MeOH and the desired material was recovered by neutralizing the resin
30 with 5% NH₄OH in MeOH. The organic phase was concentrated and filtered over a

pad of silica gel eluting with ethyl acetate. The filtrate was concentrated to dryness and the resulting solid was recrystallized with a ethyl acetate/hexane mixture to give 54 mg of the title compound as off-white solid.

¹H NMR (acetone-d₆) δ 4.37 (s, 3H), 5.97 (s, 2H), 7.00 (t, 2H), 7.15 (t, 1H), 7.21 (dd, 2H), 7.34 (m, 2H), 7.57 (d, 1H), 7.92 (d, 1H), 8.25 (dd, 1H), 8.30 (dd, 1H), 8.86 (dd, 1H), 9.79 (s, 1H). MS (+APCI) m/z 377.4 (M+H)⁺.

Step 2:

The title compound was prepared from 102 mg of methyl 1-[(4-fluorophenyl)methyl]-3-hydroxyindole-2-carboxylate and 50 mg of cyclopropanemethanol according to example 164 to yield 111 mg of a yellow solid.

¹H NMR (acetone-d₆) δ 0.43 (m, 2H), 0.65 (m, 2H), 1.46 (m, 1H), 4.41 (d, 2H), 5.98 (s, 2H), 7.00 (t, 2H), 7.14 (t, 1H), 7.21 (dd, 2H), 7.34 (m, 2H), 7.56 (d, 1H), 7.85 (d, 1H), 8.29 (m, 2H), 8.88 (d, 1H), 10.08 (s, 1H). MS (+APCI) m/z 416.4 (M+H)⁺.

EXAMPLE 12

{1-[(4-FLUOROPHENYL)METHYL]-3-(4-PYRIDYLMETHOXY)INDOL-2-YL}-
N-(3-PYRIDYL)FORMAMIDE (COMPOUND 162)

The title compound was prepared from 102 mg of methyl 1-[(4-fluorophenyl)methyl]-3-hydroxyindole-2-carboxylate and 59 mg of 4-pyridyl carbinol according to example 11, step 1, to yield 56 mg of a red solid.

¹H NMR (acetone-d₆) δ 5.63 (s, 2H), 5.94 (s, 2H), 7.01 (t, 2H), 7.18 (m, 3H), 7.30 (dd, 1H), 7.35 (t, 1H), 7.54 (d, 2H), 7.59 (d, 1H), 7.89 (d, 1H), 8.08 (dt, 1H), 8.28 (dd, 1H), 8.60 (dd, 2H), 8.65 (d, 1H), 9.62 (s, 1H). MS (+APCI) m/z 453.3 (M+H)⁺.

EXAMPLE 13

{1-[(4-FLUOROPHENYL)METHYL]-3-[(3-METHOXYPHENYL)METHOXY]INDOL-2-YL}-N-(3-PYRIDYL)

FORMAMIDE (COMPOUND 22)

The title compound was prepared from 102 mg of methyl 1-[(4-fluorophenyl)methyl]-3-hydroxyindole-2-carboxylate and 94 mg of 3-methoxybenzyl alcohol according to example 164 to yield 63 mg of a white solid.

5 ^1H NMR (acetone- d_6) δ 5.57 (s, 2H), 5.96 (s, 2H), 6.94 (dd, 1H), 7.00 (t, 2H), 7.05-7.25 (m, 5H), 7.28 (m, 2H), 7.35 (t, 1H), 7.58 (d, 1H), 7.98 (t, 2H), 8.25 (dd, 1H), 8.52 (d, 1H), 9.66 (s, 1H). MS (+APCI) m/z 482.3 (M+H) $^+$.

EXAMPLE 14

10 {5-BROMO-1-[(4-FLUOROPHENYL)METHYL]-3-(PHENYLMETHOXY)INDOL-2-YL}-*N*-(3-PYRIDYL) FORMAMIDE (COMPOUND 134)

Step 1: Ethyl 5-bromo-3-formylindole-2-carboxylate

In a 1 L round bottom flask 10.5 mL of phosphorus oxychloride was
15 added to 15.5 g of *N*-methylformanilide at room temperature that resulted in a yellow solid after 15 min. At this time, 170 mL of 1,2-dichloroethane and 20.1 g of ethyl 5-bromoindole-2-carboxylate were added. The resulting suspension was heated under reflux for 4 hours and then concentrated to remove the organic solvent. 75 g of sodium acetate in 750 mL of water were added and the solid suspension was stirred
20 for 30 min at room temperature, filtered and washed 3 times with water. The crude material was dried under vacuum for 1 hour and swished with 500 mL of EtOH to yield 21.2 g of the title compound as off-white solid.

^1H NMR (acetone- d_6) δ 1.43 (t, 3H), 5.50 (q, 2H), 7.52 (dd, 1H), 7.58 (d, 1H), 8.52 (d, 1H), 10.68 (s, 1H), 11.86 (s, 1H).

25

Step 2: Ethyl 5-bromo-3-hydroxyindole-2-carboxylate

A mixture of 21.24 g of the previous aldehyde and 14.42 g of *p*-toluenesulphonic acid monohydrate in 1 L of CH_2Cl_2 was maintained at 12-13°C and treated portionwise with 17.01 g of dried 3-chloroperoxybenzoic acid (87% purity).
30 The reaction mixture was stirred at this temperature for 2.5 hours (reaction was

monitored by TLC), quenched with 3 mL of dimethyl sulfide and poured 30 min later into a saturated aqueous bicarbonate solution. The product was extracted with CH_2Cl_2 , washed twice with saturated aqueous bicarbonate, brine and dried over anhydrous Na_2SO_4 . The organic solvent was removed under vacuum and the crude material was hydrolyzed by treatment with 10 mL of Et_3N in 300 mL of EtOH and heating to 70°C for 30 min. The organic solvent was removed under vacuum and the crude material was dissolved in ethyl acetate and washed twice with 0.5 N HCl , brine and dried over anhydrous Na_2SO_4 . The organic phase was concentrated and filtered over a pad of silica gel eluting with hot toluene. The organic phase was concentrated to dryness and the solid was swished with ethyl acetate and hexane to give 18.14 g of the title compound as a grey solid (>97% purity).

^1H NMR (acetone- d_6) δ 1.35 (t, 3H), 4.39 (q, 2H), 7.35 (dd, 1H), 7.39 (dd, 1H), 7.79 (t, 1H), 8.24 (s, 1H), 10.23 (s, 1H).

15 Step 3: Ethyl 5-bromo-3-(phenylmethoxy)indole-2-carboxylate

To a solution containing 2.04 g of ethyl 5-bromo-3-hydroxyindole-2-carboxylate, 3.94 g of benzyl alcohol and 3.34 g of di-*tert*-butyl azodicarboxylate in 30 mL of THF and 15 mL of CH_2Cl_2 at -78°C was treated dropwise with a solution containing 3.81 g of triphenylphosphine in 15 mL of CH_2Cl_2 . The resulting reaction mixture was warmed slowly to 0°C upon consumption of the starting material (monitored by TLC). 800 μL of acetic acid was added and after 30 min the solvents were removed under vacuum and the excess of acetic acid was removed by coevaporation with toluene. The crude product was filtered over a pad of silica gel eluting with CH_2Cl_2 . The organic phase was concentrated to dryness and the solid was swished with hexane to give 2.13 g of the title compound as a white solid.

^1H NMR (acetone- d_6) δ 1.36 (t, 3H), 4.38 (q, 2H), 5.30 (s, 2H), 7.30-7.40 (m, 5H), 7.56 (d, 2H), 7.76 (d, 1H), 10.56 (s, 1H). MS (+APCI) m/z 376.2, 374.1 ($\text{M}+\text{H}$) $^+$.

Step 4: Ethyl 5-bromo-1-[(4-fluorophenyl)methyl]-3-(phenylmethoxy)indole-2-carboxylate

To a mixture of 5.57 g of ethyl 5-bromo-3-(phenylmethoxy)indole-2-carboxylate and 2.9 mL of 4-fluorobenzyl bromide in 40 mL of DMF at 0°C was
5 added 887 mg of a NaH suspension (60% in oil) and the resulting reaction mixture was warmed slowly to room temperature with continuous stirring. After 0.5 hour, the reaction was quenched with saturated aqueous NH₄Cl and extracted twice with ethyl acetate/ether 1:1. The organic phase was washed with water (4 x), brine and dried over anhydrous Na₂SO₄. Flash chromatography (toluene) and recrystallization from
10 hexane yielded 5.99 g of the title compound as a white solid.

¹H NMR (acetone-d₆) δ 1.29 (t, 3H), 4.33 (q, 2H), 5.26 (s, 2H), 5.79 (s, 2H), 7.00-7.10 (m, 4H), 7.30-7.40 (m, 4H), 7.51 (m, 3H), 7.78 (s, 1H). MS (+APCI) m/z 484.3, 482.2 (M+H)⁺.

15 Step 5: {5-Bromo-1-[(4-fluorophenyl)methyl]-3-(phenylmethoxy)indol-2-yl}-N-(3-pyridyl)formamide

To a solution of 1.06 g of the above ester in 5 mL of THF 40 mL of a solution of lithium 3-pyridylamide (0.3 M in THF) was added and allowed to stir at room temperature. After consumption of the starting ester, the organic solvents were
20 removed under vacuum, aqueous acetic acid (0.05 M) was added and the product was extracted with ethyl acetate. The organic layer was washed 3 times with aqueous acetic acid (0.05 M), water (3 x), brine and dried over anhydrous Na₂SO₄. The organic phase was concentrated and filtered over a pad of silica gel eluting with ethyl acetate. The organic phase was concentrated to dryness and the solid was swished
25 with ethyl acetate and hexane to give 1.16 g of the title compound as a white solid.

¹H NMR (acetone-d₆) δ 5.58 (s, 2H), 5.95 (s, 2H), 7.01 (td, 2H), 7.17 (dd, 2H), 7.27 (dd, 1H), 7.38 (m, 3H), 7.44 (dd, 1H), 7.55 (m, 3H), 7.97 (m, 1H), 8.11 (d, 1H), 8.27 (dd, 1H), 8.50 (d, 1H), 9.62 (s, 1H). MS (+APCI) m/z 532.3, 530.2 (M+H)⁺. Anal. Calcd for C₂₈H₂₁BrFN₃O₂: C, 63.41; H, 3.99; N, 7.92. Found: C,
30 63.12; H, 4.31; N, 7.98.

EXAMPLE 15

{1-[(4-FLUOROPHENYL)METHYL]-5-(1-HYDROXY-ISOPROPYL)-3-(PHENYLMETHOXY)INDOL-2-YL}-N-(3-PYRIDYL)

FORMAMIDE (COMPOUND 130)

To a solution of 201 mg of {5-Bromo-1-[(4-fluorophenyl)methyl]-3-(phenylmethoxy)indol-2-yl}-*N*-(3-pyridyl)formamide in 10 mL of THF at -100°C was added 0.5 mL of *n*-BuLi (1.6 M in hexanes) and the mixture was stirred at -100°C for 30 min. To this cold solution, 190 μL of acetone was added and the reaction mixture was allowed to warm to room temperature. At this time, aqueous NH_4Cl was added, the product was extracted with ethyl acetate and the organic phase was washed with brine and dried over anhydrous Na_2SO_4 . Flash chromatography (100% hexane to hexane/ethyl acetate 1:2) and swish with CH_2Cl_2 /hexane yielded 61 mg of the title compound as a yellow solid.

¹H NMR (acetone-d₆) δ 1.58 (s, 6H), 4.14 (s, 1H), 5.59 (s, 2H), 5.93 (s, 2H), 7.00 (t, 2H), 7.18 (m, 2H), 7.24 (dd, 1H), 7.38 (m, 3H), 7.45-7.55 (m, 4H), 7.95 (d, 1H), 8.08 (dd, 1H), 8.24 (dd, 1H), 8.46 (d, 1H), 9.65 (s, 1H). MS (+APCI) m/z 510.4 (M+H)⁺.

EXAMPLE 16

1-[(4-FLUOROPHENYL)METHYL]-3-(PHENYLMETHOXY)-2-(N-(3-PYRIDYL)CARBAMOYL)INDOLE-5-CARBOXYLIC ACID (COMPOUND 131)

To a solution of 201 mg of {5-Bromo-1-[(4-fluorophenyl)methyl]-3-(phenylmethoxy)indol-2-yl}-*N*-(3-pyridyl)formamide in 10 mL of THF at -100°C was added 0.5 mL of *n*-BuLi (1.6 M in hexanes) and the mixture was stirred at -100°C for 30 min. CO_2 was introduced to the reaction mixture and warmed to room temperature. The reaction was quenched with 150 μL of acetic acid and poured into a saturated aqueous NH_4Cl solution. The product was extracted with ethyl acetate and the organic phase was washed with brine and dried over anhydrous Na_2SO_4 . The

organic phase was concentrated and the crude solid was swished with ethyl acetate to give 75 mg of the title compound as a white solid (>95% purity).

¹H NMR (dmso-d₆) δ 5.42 (s, 2H), 5.76 (s, 2H), 7.08 (m, 4H), 7.25-7.35 (m, 4H), 7.40 (d, 2H), 7.69 (d, 1H), 7.87 (d, 1H), 7.98 (d, 1H), 8.28 (d, 1H), 8.46 (s, 1H), 8.61 (s, 1H), 10.12 (s, 1H), 12.76 (s, 1H). MS (+APCI) m/z 496.5 (M+H)⁺.

EXAMPLE 17

{1-[(4-FLUOROPHENYL)METHYL]-4-(1-HYDROXY-ISOPROPYL)-3-(PHENYLMETHOXY)INDOL-2-YL}-N-(3-PYRIDYL)

10

FORMAMIDE (COMPOUND 94)

Step 1: Ethyl 4-bromo-indolecarboxylate

A solution of 23 mL of ethyl azidoacetate and 7.6 mL of 2-bromobenzaldehyde in 40 mL ethanol was added dropwise to a solution of 4.5 g sodium in 180 mL ethanol, in a bath at -10°C, at a rate such that the reaction temperature does not rise above 8°C. After the addition is complete, the mixture is stirred at 5-10°C for 30 min. The reaction mixture is then poured into a mixture of 28 g of NH₄Cl in 1 L ice, and extracted with 1:4 CH₂Cl₂/hexane. The organic phase is filtered through 150 mL silica gel, which is rinsed with 200 mL of the same solvent. This is evaporated to near dryness, diluted with 300 mL xylene, and stabilised with 60 mg of 2,5-di-t-butylhydroquinone. This mixture is heated with a distillation head until 50 mL of xylene has distilled. The mixture is cooled and evaporated in vacuo to a volume of 80 mL, which is diluted with 80 mL of hexane. A white solid forms upon cooling to 0°C, which is filtered off.

¹H NMR (acetone-d₆) δ 1.37 (t, 3H), 4.37 (q, 2H), 7.13 (t, 1H), 7.21 (t, 1H), 7.33 (d, 1H), 7.55 (d, 1H), 11.3 (s, 1H).

EXAMPLE 18

{1-[(4-FLUOROPHENYL)METHYL]-6-(1-HYDROXY-ISOPROPYL)-3-(PHENYLMETHOXY)INDOL-2-YL}-N-(3-PYRIDYL)

30

FORMAMIDE (COMPOUND 118)

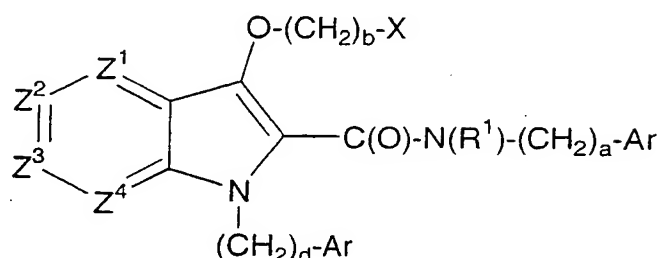
Step 1: Ethyl 6-bromo-indolecarboxylate

Using the method described in example 17, Step 1, starting with 4-bromobenzaldehyde, the title compound is obtained as a white solid.

¹H NMR (acetone-d₆) δ 1.35 (t, 3H), 4.35 (q, 2H), 7.18 (s, 1H), 7.24 (d, 1H), 7.64 (d, 1H), 7.73 (s, 1H), 11.10 (s, 1H).

WHAT IS CLAIMED IS:

1. A compound represented by formula I:



5

I

or a pharmaceutically acceptable salt or hydrate thereof wherein:

one of Z^1 , Z^2 , Z^3 and Z^4 represents N or CR^2 and the others represent CR^2 ;

a represents 0 or 1;

b represents 0, 1 or 2;

10

d represents 0, 1 or 2;

R^1 represents H, C_{1-4} alkyl or hydroxy C_{1-4} alkyl;

each R^2 is independently selected from the group consisting of:

H, halo, C_{1-8} alkyl, halo C_{1-8} alkyl, hydroxy C_{1-8} alkyl, CN, Het, OR^a , $\text{OC}(\text{O})\text{N}(\text{R}^b)_2$,

$\text{NR}^b\text{C}(\text{O})\text{R}^a$, $\text{C}(\text{R}^a)_2\text{CO}_2\text{R}^a$, C_{1-8} alkyl $\text{N}(\text{R}^b)_2$, halo C_{1-8} alkyl $\text{N}(\text{R}^b)_2$, CO_2R^a ,

15 $\text{C}(\text{O})\text{N}(\text{R}^b)_2$, $\text{SO}_2\text{N}(\text{R}^b)_2$, $\text{S}(\text{O})_b\text{R}^d$ and $\text{NR}^b\text{SO}_2\text{R}^d$;

each R^a is independently selected from H, C_{1-4} alkyl,

C_{1-4} alkyl NHC_{1-4} alkyl, and C_{1-4} alkyl $\text{N}(\text{C}_{1-4}$ alkyl) $_2$, the alkyl portions of which are optionally substituted with 1-3 halo groups;

each R^b is selected from H and C_{1-7} alkyl, and when two R^b 's are

20

present, they can be taken together and represent a fused ring system having 5-10 members, said ring system being saturated or containing 1-4 double bonds, and optionally including 1-3 heteroatoms selected from O, S and NR^e ;

R^d and R^e are independently selected from Het, C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, and C_{1-7} alkyl-Het;

25

Het represents a 5-10 membered aromatic, partially aromatic or non-aromatic ring system containing 1-4 heteroatoms selected from O, S and N, optionally substituted on any available position with oxo, C_{1-4} alkyl, halo, amino, hydroxy C_{1-4} alkyl, halo C_{1-4} alkyl and amino C_{1-4} alkyl;

X represents C₃-7cycloalkyl or Ar;

and each Ar is independently selected from the group consisting of:
phenyl, thienyl, thiazolyl, pyridyl, oxazolyl, tetrazolyl, pyrimidinyl, pyrazinyl and
pyridazinyl,

5 said Ar being optionally substituted with 1-4 members selected from:
halo, hydroxy, CN, C₁-4alkyl, C₁-6haloalkyl, C₁-6hydroxyalkyl, OC₁-6alkyl,
OC₁-6haloalkyl, OC₁-6hydroxyalkyl, C₁-6alkylOC₁-6alkyl, C₁-6alkylOC₁-
6haloalkyl, C(O)NH₂, C(O)NHC₁-6alkyl, C(O)N(C₁-6alkyl)₂, C₁-6 alkylOC₁-
6alkylC(O)NH₂, CO₂H, CO₂C₁-6alkyl, NHC(O)C₁-6alkyl, NHC(O)OC₁-6alkyl, and
10 SO₂C₁-6alkyl.

2. A compound in accordance with claim 1 wherein Z¹, Z², Z³
and Z⁴ represent CR².

15 3. A compound in accordance with claim 1 wherein b represents 0
or 1.

4. A compound in accordance with claim 1 wherein d represents
1.

20 5. A compound in accordance with claim 1 wherein R¹ represents
H or CH₃.

25 6. A compound in accordance with claim 1 wherein each R² is
independently selected from the group consisting of H, C₁-8alkyl, hydroxyC₁-8alkyl,
CO₂R^a, C₁-8alkylN(R^b)₂ and C(O)N(R^b)₂;
and R^b is selected from H and C₁-3 alkyl.

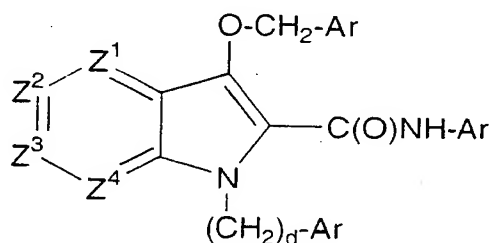
30 7. A compound in accordance with claim 1 wherein X represents
Ar and Ar is independently selected from the group consisting of: phenyl, pyridyl and
tetrazolyl,

 said Ar being optionally substituted with 1-4 members selected from:
halo, CN, C₁-4alkyl, C₁-6haloalkyl, OC₁-6alkyl, OC₁-6haloalkyl, C₁-6hydroxyalkyl,

C(O)NH₂, C(O)NHC₁₋₆alkyl, C(O)N(C₁₋₆alkyl)₂, CO₂H, CO₂C₁₋₆alkyl, NHC(O)C₁₋₆alkyl, NHC(O)OC₁₋₆alkyl and SO₂C₁₋₆alkyl.

8. A compound in accordance with claim 1 wherein:
 5 Z¹, Z², Z³ and Z⁴ represent CR²;
 each R² is independently selected from the group consisting of H, C₁₋₈alkyl, hydroxyC₁₋₈alkyl, CO₂R^a, C₁₋₈alkylN(R^b)₂ and C(O)N(R^b)₂ wherein R^b is selected from H and C₁₋₃ alkyl;
 b represents 0 or 1;
 10 d represents 1;
 R¹ represents H or CH₃;
 X represents Ar and
 Ar is independently selected from the group consisting of: phenyl, pyridyl and tetrazolyl, said Ar being optionally substituted with 1-4 members selected
 15 from: halo, CN, C₁₋₄alkyl, C₁₋₆haloalkyl, OC₁₋₆alkyl, OC₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, C(O)NH₂, C(O)NHC₁₋₆alkyl, C(O)N(C₁₋₆alkyl)₂, CO₂H, CO₂C₁₋₆alkyl, NHC(O)C₁₋₆alkyl, NHC(O)OC₁₋₆alkyl and SO₂C₁₋₆alkyl.

9. A compound represented by Formula Ia:



Ia

wherein all variables are as defined in claim 1.

10. A compound in accordance with claim 9 wherein Z¹, Z², Z³ and Z⁴ represent CR².

11. A compound in accordance with claim 9 wherein each R² is independently selected from the group consisting of H, C₁₋₈alkyl, hydroxyC₁₋₈alkyl,

CO₂R^a: C₁₋₈alkylN(R^b)₂ and C(O)N(R^b)₂ wherein R^a is independently selected from H and C₁₋₄alkyl, and R^b is selected from H and C₁₋₃ alkyl.

12. A compound in accordance with claim 9 wherein each Ar is selected from phenyl, pyridyl and tetrazolyl, optionally substituted with 1-4 members selected from: halo, CN, C₁₋₄alkyl, C₁₋₆haloalkyl, OC₁₋₆alkyl, OC₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, C(O)NH₂, C(O)NHC₁₋₆alkyl, C(O)N(C₁₋₆alkyl)₂, CO₂H, CO₂C₁₋₆alkyl, NHC(O)C₁₋₆alkyl, NHC(O)OC₁₋₆alkyl and SO₂C₁₋₆alkyl.
13. A compound in accordance with claim 1 in accordance with the following table:

<p style="text-align: center;">I</p>				
Cpd	Z's	(CH ₂) _b -(O) _a -(CH ₂) _b -X	N(R ¹)(CH ₂) _a -Ar	(CH ₂) _d -Ar
1	CH	OCH ₂ -Phe-4-F	N(Me)-3-Pyr	Bnzl
2	CH	OCH ₂ -Phe-4-F	N(Me)-4-Pyr	Bnzl
3	CH	OCH ₂ -Phe-4-F	N(Me)-Phe-3,4-di-OMe	Bnzl
4	CH	OCH ₂ -Phe-4-F	N(Me)-Phe-3,4-di-F	Bnzl
5	CH	OCH ₂ -Phe-4-F	N(Me)-5-Pyr-2-OMe	Bnzl
6	CH	OCH ₂ -Phe-4-F	N(Me)-5-tetrazolyl	Bnzl

7	CH	OCH ₂ -Phe-4-F	N(Me)-4-Pyr-2-OMe	Bnzl
8	CH	OCH ₂ -Phe-4-F	N(Me)-5-Pyr-2-CN	Bnzl
9	CH	OCH ₂ -Phe-4-F	N(Me)-4-Pyr-2-OMe	Bnzl
10	CH	O-Bnzl	NH-Phe-3,4-di-OMe	Bnzl-4-F
11	CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
12	CH	OCH ₂ -Phe-3-OCF ₂ H	NH-3-Pyr	Bnzl-3-OCF ₂ H
13	CH	OCH ₂ -Phe-3-OCF ₂ H	NH-4-Pyr	Bnzl-3-OCF ₂ H
14	CH	OCH ₂ -Phe-3-OCF ₂ H	NH-Phe-3,4-di-OMe	Bnzl-3-OCF ₂ H
15	CH	OCH ₂ -Phe-3-OCF ₂ H	NH-Phe-3,4-di-F	Bnzl-3-OCF ₂ H
16	CH	O-Bnzl	NH-3-Pyr	Bnzl-4-OCF ₂ H
17	CH	OCH ₂ -Phe-3-OMe	NH-3-Pyr	Bnzl-4-OCF ₂ H
18	CH	OCH ₂ -Phe-3-OMe	NH-5-tetrazolyl	Bnzl-4-OCF ₂ H
19	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr-2-OMe	Bnzl-4-OCF ₂ H
20	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr	Bnzl-4-OCF ₂ H
21	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr-2-NHC(O)Me	Bnzl-4-OCF ₂ H
22	CH	OCH ₂ -Phe-3-OMe	NH-3-Pyr	Bnzl-4-F
23	CH	OCH ₂ -Phe-3-OMe	NH-5-tetrazolyl	Bnzl-4-F
24	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr-2-OMe	Bnzl-4-F
25	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr	Bnzl-4-F
26	CH	OCH ₂ -Phe-3-OMe	NH-4-Pyr-2-NHC(O)Me	Bnzl-4-F

27	CH	OCH ₂ -Phe-3-OMe	NH-5-pyrimidinyl	Bnzl-4-F
28	CH	O-Bnzl	NH-3-Pyr	Bnzl-3,4-di-F
29	CH	O-Bnzl	NH-4-Pyr	Bnzl-3,4-di-F
30	CH	O-Bnzl	NH-Phe-3,4-di-OMe	Bnzl-3,4-di-F
31	CH	O-Bnzl	NH-Phe-3,4-di-F	Bnzl-3,4-di-F
32	CH	O-Bnzl	NH-5-Pyr-2-OMe	Bnzl-3,4-di-F
33	CH	O-Bnzl	NH-5-tetrazolyl	Bnzl-3,4-di-F
34	CH	O-Bnzl	NH-4-Pyr-2-OMe	Bnzl-3,4-di-F
35	CH	O-Bnzl	NH-5-Pyr-2-CN	Bnzl-3,4-di-F
36	CH	O-Bnzl	NH-5-Pyr-2-NHC(O)Me	Bnzl-3,4-di-F
37	CH	OCH ₂ -4-Pyr	NH-3-Pyr	Bnzl-4-CF ₃
38	CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-CF ₃
39	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-OMe	Bnzl-4-CF ₃
40	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-F	Bnzl-4-CF ₃
41	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-OMe	Bnzl-4-CF ₃
42	CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-CF ₃
43	CH	OCH ₂ -4-Pyr	NH-4-Pyr-2-OMe	Bnzl-4-CF ₃
44	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-CN	Bnzl-4-CF ₃
45	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-NHC(O)Me	Bnzl-4-CF ₃
46	CH	OCH ₂ -4-Pyr	NH-3-Pyr	Bnzl
47	CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl
48	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-OMe	Bnzl

49	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-F	Bnzl
50	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-OMe	Bnzl
51	CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl
52	CH	OCH ₂ -4-Pyr	NH-4-Pyr-2-OMe	Bnzl
53	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-CN	Bnzl
54	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-NHC(O)Me	Bnzl
55	CH	OCH ₂ -4-Pyr	NH-4-Pyr-2-NHC(O)OEt	Bnzl
56	CH	O-Bnzl	NH-3-Pyr	Bnzl
57	CH	O-Bnzl	NH-4-Pyr	Bnzl
58	CH	O-Bnzl	NH-Phe-3,4-di-OMe	Bnzl
59	Z ^I =N, all others =CH	O-Bnzl	NH-Phe-3,4-di-F	Bnzl
60	Z ^I =N, all others =CH	O-Bnzl	NH-5-Pyr-2-OMe	Bnzl
61	CH	O-Bnzl	NH-5-tetrazolyl	Bnzl
62	CH	O-Bnzl	NH-4-Pyr-2-OMe	Bnzl
63	CH	O-Bnzl	NH-5-Pyr-2-CN	Bnzl
64	CH	O-Bnzl	NH-5-Pyr-2-NHC(O)Me	Bnzl
65	CH	O-Bnzl	NH-4-Pyr-2-NHC(O)OEt	Bnzl
66	CH	OCH ₂ -4-Pyr	NH-3-Pyr	Bnzl-4-OCF ₂ H
67	CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-OCF ₂ H
68	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-OMe	Bnzl-4-OCF ₂ H
69	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-F	Bnzl-4-OCF ₂ H
70	Z ^I =N, all others =CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-OMe	Bnzl-4-OCF ₂ H

71	$Z^1=N$, all others $=CH$	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- OCF_2H
72	$Z^1=N$, all others $=CH$	$OCH_2-4-Pyr$	NH-4-Pyr-2-OMe	Bnzl-4- OCF_2H
73	CH	O-Bnzl	NH-3-Pyr	Bnzl-4-Me
74	CH	$OCH_2-4-Pyr$	NH-5-Pyr-2-CN	Bnzl-4- OCF_2H
75	CH	$OCH_2-4-Pyr$	NH-5-Pyr-2- NHC(O)Me	Bnzl-4- OCF_2H
76	$Z^4=$ $CC(Me)_2OH$ all others $=CH$	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3
77	$Z^4=$ CCO_2H all others $=CH$	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3
78	$Z^4=$ CCH_2NMe_2 all others $=CH$	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3
79	$Z^4=$ $CC(O)NMe_2$ all others $=CH$	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3
80	$Z^4=CBr$ all others $=CH$	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3
81	$Z^4=$ CSO_2NH_2 all others $=CH$	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3
82	$Z^1=$ $CC(Me)_2OH$ all others $=CH$	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3
83	$Z^1=$ CCO_2H all others $=CH$	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3

84	$Z^1 =$ CCH_2NMe_2 all others=CH	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3
85	$Z^1 =$ $CC(O)NMe_2$ all others=CH	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3
86	$Z^1 = CBr$ all others=CH	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3
87	$Z^1 =$ CSO_2NH_2 all others=CH	$OCH_2-4-Pyr$	NH-5-tetrazolyl	Bnzl-4- CF_3
88	$Z^1 =$ $CC(Me)_2OH$ all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
89	$Z^1 =$ CCO_2H all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
90	$Z^1 =$ CCH_2NMe_2 all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
91	$Z^1 =$ $CC(O)NMe_2$ all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
92	$Z^1 = CBr$ all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
93	$Z^1 =$ CSO_2NH_2 all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
94	$Z^1 =$ $CC(Me)_2OH$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F

95	$Z^1 =$ CCO_2H all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
96	$Z^1 =$ CCH_2NMe_2 all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
97	$Z^1 =$ $CC(O)NMe_2$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
98	$Z^1 = CBr$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
99	$Z^1 =$ CSO_2NH_2 all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
100	$Z^4 =$ $CC(Me)_2OH$ all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
101	$Z^4 =$ CCO_2H all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
102	$Z^4 =$ CCH_2NMe_2 all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
103	$Z^4 =$ $CC(O)NMe_2$ all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
104	$Z^4 = CBr$ all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
105	$Z^4 =$ CSO_2NH_2 all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3

106	$Z^4 =$ CC(Me) ₂ OH all others=CH	O-BnzI	NH-3-Pyr	BnzI-4-F
107	$Z^4 =$ CCO ₂ H all others=CH	O-BnzI	NH-3-Pyr	BnzI-4-F
108	$Z^4 =$ CCH ₂ NMe 2 all others=CH	O-BnzI	NH-3-Pyr	BnzI-4-F
109	$Z^4 =$ CC(O)NMe ₂ all others=CH	O-BnzI	NH-3-Pyr	BnzI-4-F
110	$Z^4 =$ CBr all others=CH	O-BnzI	NH-3-Pyr	BnzI-4-F
111	$Z^4 =$ CSO ₂ NH ₂ all others=CH	O-BnzI	NH-3-Pyr	BnzI-4-F
112	$Z^3 =$ CC(Me) ₂ OH all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	BnzI-4-CF ₃
113	$Z^3 =$ CCO ₂ H all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	BnzI-4-CF ₃
114	$Z^3 =$ CCH ₂ NMe ₂ all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	BnzI-4-CF ₃
115	$Z^3 =$ CC(O)NMe ₂ all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	BnzI-4-CF ₃
116	$Z^3 =$ CBr all others=CH	OCH ₂ -4-Pyr	NH-4-Pyr	BnzI-4-CF ₃

117	$Z^3 =$ CSO_2NH_2 all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
118	$Z^3 =$ $CC(Me)_2OH$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
119	$Z^3 =$ CCO_2H all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
120	$Z^3 =$ CCH_2NMe_2 all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
121	$Z^3 =$ $CC(O)NMe_2$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
122	$Z^3 = CBr$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
123	$Z^3 =$ CSO_2NH_2 all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
124	$Z^2 =$ $CC(Me)_2OH$ all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
125	$Z^2 =$ CCO_2H all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
126	$Z^2 =$ CCH_2NMe_2 all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3
127	$Z^2 =$ $CC(O)NMe_2$ all others=CH	$OCH_2-4-Pyr$	NH-4-Pyr	Bnzl-4- CF_3

128	$Z^2 = \text{CBr}$ all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
129	$Z^2 =$ CSO_2NH_2 all others=CH	$\text{OCH}_2\text{-4-Pyr}$	NH-4-Pyr	Bnzl-4- CF_3
130	$Z^2 =$ $\text{CC}(\text{Me})_2\text{OH}$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
131	$Z^2 =$ CCO_2H all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
132	$Z^2 =$ CCH_2NMe_2 all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
133	$Z^2 =$ $\text{CC}(\text{O})\text{NMe}_2$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
134	$Z^2 = \text{CBr}$ all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
135	$Z^2 =$ CSO_2NH_2 all others=CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
136	CH	O-Bnzl	NH-3-Pyr	Bnzl-4- $\text{C}(\text{Me})_2\text{-OH}$
137	CH	$\text{OCH}_2\text{-3-Pyr}$	NH-3-Pyr	Bnzl-4-F
138	CH	$\text{OCH}_2\text{-3-Pyr}$	NH-4-Pyr	Bnzl-4-F
139	CH	$\text{OCH}_2\text{-3-Pyr}$	NH-Phe-3,4-di- OMe	Bnzl-4-F
140	CH	$\text{OCH}_2\text{-3-Pyr}$	NH-Phe-3,4-di-F	Bnzl-4-F
141	CH	$\text{OCH}_2\text{-3-Pyr}$	NH-5-Pyr-2-OMe	Bnzl-4-F
142	CH	O-Bnzl	NH-3-Pyr	Bnzl-4- CO_2Me
143	CH	$\text{OCH}_2\text{-3-Pyr}$	NH-5-tetrazolyl	Bnzl-4-F

144	CH	OCH ₂ -3-Pyr	NH-4-Pyr-2-OMe	Bnzl-4-F
145	CH	OCH ₂ -3-Pyr	NH-5-Pyr-2-CN	Bnzl-4-F
146	CH	OCH ₂ -3-Pyr	NH-5-Pyr-2- NHC(O)Me	Bnzl-4-F
147	CH	O-Bnzl	NH-Phe-3-SO ₂ Me	Bnzl-4-F
148	CH	O-Bnzl	NH-3-Pyr	Bnzl-4-CF ₃
149	CH	O-CH ₂ -cPr	NH-Phe-3,4-di- OMe	Bnzl-4-t-Bu
150	CH	O-CH ₂ -cPr	NH-5-tetrazolyl	Bnzl-4-t-Bu
151	CH	O-CH ₂ -cPr	NH-4-Pyr-2-OMe	Bnzl-4-t-Bu
152	CH	O-CH ₂ -cPr	NH-5-Pyr-2-OMe	Bnzl-4-t-Bu
153	CH	O-CH ₂ -cPr	NH-4-Pyr-2- NHC(O)OEt	Bnzl-4-t-Bu
154	CH	O-CH ₂ -cPr	NH-3-Pyr	Bnzl-4-F
155	CH	O-CH ₂ -cPr	NH-4-Pyr	Bnzl-4-F
156	CH	O-CH ₂ -cPr	NH-Phe-3,4-di- OMe	Bnzl-4-F
157	CH	O-CH ₂ -cPr	NH-Phe-3,4-di-F	Bnzl-4-F
158	CH	O-CH ₂ -cPr	NH-5-Pyr-2-OMe	Bnzl-4-F
159	CH	O-CH ₂ -cPr	NH-5-tetrazolyl	Bnzl-4-F
160	CH	O-CH ₂ -cPr	NH-4-Pyr-2-OMe	Bnzl-4-F
161	CH	O-CH ₂ -cPr	NH-5-Pyr-2- NHC(O)Me	Bnzl-4-F
162	CH	OCH ₂ -4-Pyr	NH-3-Pyr	Bnzl-4-F
163	CH	OCH ₂ -4-Pyr	NH-4-Pyr	Bnzl-4-F
164	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di- OMe	Bnzl-4-F
165	CH	OCH ₂ -4-Pyr	NH-Phe-3,4-di-F	Bnzl-4-F
166	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-OMe	Bnzl-4-F
167	CH	OCH ₂ -4-Pyr	NH-5-tetrazolyl	Bnzl-4-F
168	CH	OCH ₂ -4-Pyr	NH-4-Pyr-2-OMe	Bnzl-4-F
169	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2-CN	Bnzl-4-F
170	CH	OCH ₂ -4-Pyr	NH-5-Pyr-2- NHC(O)Me	Bnzl-4-F

171	CH	OCH ₂ -4-Pyr	NH-4-Pyr-2-NHC(O)OEt	Bnzl-4-F
172	CH	O-Bnzl	NH-3-Pyr	Bnzl-4-t-Bu
173	CH	O-Bnzl	NH-3-Pyr	Bnzl-4-F
174	CH	O-Bnzl	NH-4-Pyr	Bnzl-4-F
175	CH	O-Bnzl	NH-Phe-3,4-di-OMe	Bnzl-4-F
176	CH	O-Bnzl	NH-Phe-3,4-di-F	Bnzl-4-F
177	CH	O-Bnzl	NH-5-Pyr-2-OMe	Bnzl-4-F
178	CH	O-Bnzl	NH-5-tetrazolyl	Bnzl-4-F
179	CH	O-Bnzl	NH-4-Pyr-2-OMe	Bnzl-4-F
180	CH	O-Bnzl	NH-5-Pyr-2-CN	Bnzl-4-F
181	CH	O-Bnzl	NH-5-Pyr-2-NHC(O)Me	Bnzl-4-F
182	CH	O-Bnzl	NH-4-Pyr-2-NHC(O)OEt	Bnzl-4-F
183	CH	O-Bnzl	N(Me)-3-Pyr	Bnzl-4-F
184	CH	O-Bnzl	N(Me)-3-Pyr	Bnzl-4-CF ₃
185	CH	O-Bnzl	3-pyridylmethyl	Bnzl-4-F
186	CH	O-Bnzl	4-pyridylmethyl	Bnzl-4-F
Phe=phenyl, Bzl=benzyl, Pyr=pyridyl				

or a pharmaceutically acceptable salt or hydrate thereof.

14. A compound selected from the group consisting of:
- 5 { 1-[(4-Fluorophenyl)methyl]-3-(phenylmethoxy)indol-2-yl }-N-(3-pyridyl)formamide;
{ 1-[(4-Fluorophenyl)methyl]-3-(phenylmethoxy)indol-2-yl }-N-[3-(methylsulfonyl)phenyl] formamide;
{ 1-[(4-Fluorophenyl)methyl]-3-(phenylmethoxy) indol-2-yl }-N-(3-pyridylmethyl) formamide;
 - 10 { 1-[(4-Fluorophenyl)methyl]-3-(phenylmethoxy) indol-2-yl }-N-(4-pyridylmethyl) formamide;
Methyl 4-{ [3-(phenylmethoxy)-2-(N-(3-pyridyl)carbamoyl)methyl] benzoate;

(1-{{4-(1-Hydroxyisopropyl)phenyl)methyl}-3-(phenylmethoxy) indol-2-yl}-N-(3-pyridyl) formamide;

{1-{{4-(Methylphenyl)methyl}-3-(phenylmethoxy) indol-2-yl}-N-(3-pyridyl) formamide;

5 (1-{{4-(*tert*-Butyl)phenyl)methyl}-3-(phenylmethoxy) indol-2-yl}-N-(3-pyridyl) formamide;

(1-{{4-(Trifluoromethyl)phenyl)methyl}-3-(phenylmethoxy)indol-2-yl)-N-(3-pyridyl) formamide;

(1-{{4-(Difluoromethoxy)phenyl)methyl}-3-(phenylmethoxy)indol-2-yl)-N-(3-pyridyl) formamide;

10 {3-(Cyclopropylmethoxy)-1-{{4-fluorophenyl)methyl}indol-2-yl}-N-(3-pyridyl)formamide;

{1-{{4-Fluorophenyl)methyl}-3-(4-pyridylmethoxy)indol-2-yl}-N-(3-pyridyl)formamide;

15 {1-{{4-Fluorophenyl)methyl}-3-{{3-methoxyphenyl)methoxy}indol-2-yl}-N-(3-pyridyl)formamide;

{5-Bromo-1-{{4-fluorophenyl)methyl}-3-(phenylmethoxy)indol-2-yl}-N-(3-pyridyl) formamide;

{1-{{4-Fluorophenyl)methyl}-5-(1-hydroxy-isopropyl)-3-(phenylmethoxy)indol-2-yl}-N-(3-pyridyl)formamide;

20 1-{{4-Fluorophenyl)methyl}-3-(phenylmethoxy)-2-(N-(3-pyridyl)carbamoyl)indole-5-carboxylic acid;

{1-{{4-Fluorophenyl)methyl}-4-(1-hydroxy-isopropyl)-3-(phenylmethoxy)indol-2-yl}-N-(3-pyridyl)formamide; and

25 {1-{{4-Fluorophenyl)methyl}-6-(1-hydroxy-isopropyl)-3-(phenylmethoxy)indol-2-yl}-N-(3-pyridyl)formamide,

or a pharmaceutically acceptable salt or hydrate thereof.

15. A pharmaceutical composition comprised of a compound in
30 accordance with any one of claims 1 to 14 in combination with a pharmaceutically acceptable carrier.

16. A method of treating or preventing a PDE-IV mediated disease or condition in a mammalian patient in need thereof, comprising administering said patient an amount of a compound in accordance with claim 1 that is effective for treating or preventing said PDE-IV mediated disease or condition.

5

17. A method in accordance with claim 16 wherein the disease or condition is selected from the group consisting of:

inflammatory response or muscular spasm; bladder or alimentary smooth muscle spasm; asthma; inflamed lung associated with asthma; cystic fibrosis; chronic bronchitis; eosinophilic granuloma; psoriasis; other benign and malignant proliferative skin diseases; endotoxic shock; septic shock; ulcerative colitis; Crohn's disease; reperfusion injury of the myocardium or brain; inflammatory arthritis; osteoporosis, chronic glomerulonephritis; atopic dermatitis; urticaria; adult or infant respiratory distress syndrome; diabetes; diabetes insipidus; allergic rhinitis; allergic conjunctivitis; vernal conjunctivitis; arterial restenosis and atherosclerosis.

15

18. A method in accordance with claim 16 wherein the disease or condition is selected from the group consisting of:

pain; cough; fever; rheumatoid arthritis; osteoarthritis; ankylosing spondylitis; transplant rejection; graft versus host disease; hypersecretion of gastric acid; bacterial, fungal or viral induced infection or sepsis; septic shock; cachexia and muscle wasting; depression; memory impairment; and prevention of tumor growth and invasion of normal tissues.

25

19. A phosphodiesterase IV (PDE-IV) inhibitor pharmaceutical composition comprising an acceptable PDE-IV inhibiting amount of a compound of formula I as defined in any one of claims 1 to 13 or a pharmaceutically

acceptable salt or hydrate thereof, in association with a pharmaceutically acceptable carrier.

20. Use of a compound of formula I, as defined in any one of claims 1
5 to 13, or a pharmaceutically acceptable salt or hydrate thereof, in the manufacture of a medicament for treating or preventing a PDE-IV mediated disease or condition in a mammalian patient in need thereof.

21. Use of a compound, salt or hydrate of claim 14, in the manufacture
10 of a medicament for treating or preventing a PDE-IV mediated disease or condition in a mammalian patient in need thereof.

22. A compound of formula I, as defined in any one of claims 1 to 13,
or a pharmaceutically acceptable salt thereof for use as a PDE-IV inhibitor.
15

23. A compound, salt or hydrate of claim 14 for use as a PDE-IV inhibitor.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 September 2001 (07.09.2001)

PCT

(10) International Publication Number
WO 01/64639 A3

(51) International Patent Classification⁷: C07D 209/04, 209/36, 401/04, 401/12, 401/14, 471/04, A61K 31/404, 31/437, 31/44, 31/41, A61P 11/06, 29/00 // C07D 471/04, 221:00, 209:00

(21) International Application Number: PCT/CA01/00270

(22) International Filing Date: 2 March 2001 (02.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/186,571 2 March 2000 (02.03.2000) US

(71) Applicant (for all designated States except US):
MERCK FROSST CANADA & CO. [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LABELLE, Marc** [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). **STURINO, Claudio** [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). **LACHANCE, Nicolas** [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). **MACDONALD, Dwight** [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA).

(74) Agents: **MURPHY, Kevin, P.** et al.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montreal, Québec H3A 2Y3 (CA).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EF, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

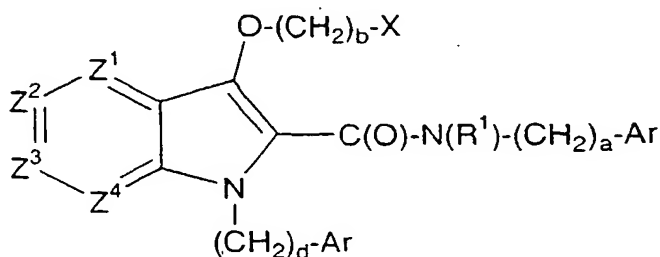
Published:

— with international search report

(88) Date of publication of the international search report:
28 February 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PDE IV INHIBITING AMIDES, COMPOSITIONS AND PHARMACEUTICAL USE



(I)

(57) Abstract: Compounds represented by formula (I), as well as pharmaceutically acceptable salts and hydrates thereof are disclosed as useful for treating or preventing diseases and conditions mediated by PDE-IV. Pharmaceutical compositions and methods of treatment are also included.

WO 01/64639 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 01/00270

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/04 C07D209/36 C07D401/04 C07D401/12 C07D401/14
 C07D471/04 A61K31/404 A61K31/437 A61K31/44 A61K31/41
 A61P11/06 A61P29/00 //(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

PAJ, WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	EP 0 186 367 A (WARNER LAMBERT CO) 2 July 1986 (1986-07-02) abstract, formula (I) page 1, line 5 - line 10 example 25	1-12, 15-23
X	P. C. UNANGST ET AL.: "Novel Indolecarboxamidotetrazoles as Potential Antiallergy Agents" JOURNAL OF MEDICINAL CHEMISTRY., vol. 32, 1989, pages 1360-1366, XP000910104 AMERICAN CHEMICAL SOCIETY., US ISSN: 0022-2623 page 1360, left-hand column, line 5 page 1361, right-hand column, paragraph "Biological Results and Discussion" table IV, compounds 8f, 8cc	1-12, 15-23

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

5 November 2001

Date of mailing of the international search report

09/11/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel: (+31-70) 340-2040, Tx. 31 651 cpo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Hoepfner, W

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 01/00270

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0186367	A	02-07-1986	US 4675332 A 23-06-1987
			AT 86252 T 15-03-1993
			AU 576131 B2 11-08-1988
			AU 5050885 A 19-06-1986
			CA 1259317 A1 12-09-1989
			CN 85109061 A , B 21-01-1987
			DE 3587148 D1 08-04-1993
			DE 3587148 T2 15-07-1993
			DK 568885 A 11-06-1986
			EP 0186367 A2 02-07-1986
			ES 549768 D0 16-04-1986
			ES 8700252 A1 01-01-1987
			FI 854821 A , B, 11-06-1986
			GR 852948 A1 11-04-1986
			IE 58554 B 06-10-1993
			JP 1925657 C 25-04-1995
			JP 6053736 B 20-07-1994
			JP 61191683 A 26-08-1986
			KR 8900292 B1 13-03-1989
			NO 854941 A , B, 11-06-1986
			NZ 214480 A 30-05-1988
			PH 24075 A 05-03-1990
			PT 81637 A , B 01-01-1986
			ZA 8508651 A 24-06-1987

THIS PAGE BLANK (USPTO)

App. No. 10/849,089
Filed: May 19, 2004
Inventor: NAZARE, et al.
Docket No. DEAV2003/0033 US NP
PRIOR ART